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(54) Title: NEW ORAL PHARMACEUTICAL DOSAGE FORM			
(57) Abstract An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more antibacterial compounds in a fixed formulation. The fixed formulation is intended for oral use and in the form of an enteric coating layered tablet, a capsule or a multiple unit tableted dosage form. The multiple unit dosage form is most preferred. The new fixed formulation is especially useful in the treatment of disorders associated with <i>Helicobacter</i> infections.			

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NEW ORAL PHARMACEUTICAL DOSAGE FORM

Field of the invention

5 The present invention is related to new oral pharmaceutical preparations especially for use in the treatment of disorders associated with *Helicobacter* infections. The present preparations comprise an acid susceptible proton pump inhibitor in combination with one or more antibacterial compounds in a new fixed unit dosage form, especially a tableted dosage form. Furthermore, the present invention refers to a method for the manufacture of
10 such preparations and the use of such preparations in medicine, especially in the treatment of *Helicobacter pylori* infections.

Background of the invention

15 The relationship between gastrointestinal disorders and infections with *Helicobacter pylori* proposed in 1983 by Warren (Warren JR Lancet 1983;1.1273) is well established today. A number of different therapies have been proposed for treatment of *H. pylori* infections. Most of these therapies comprise different combinations of antibacterial compounds. Some of these therapies also comprise a bismuth compound, see for instance WO 89/03219
20 (Borody). Other combination therapies comprise a proton pump inhibitor and one or more antibacterial compounds, for instance a combined regimen of omeprazole and amoxicillin which has been approved by regulatory authorities in for example Great Britain and Sweden for the treatment of *H. pylori* infections. Different triple therapies, for example omeprazole, clarithromycin and amoxicillin or other antibacterial substances, have recently
25 been reported at the 10th World Congresses of Gastroenterology in October 1994. Some published patent applications in this field are for instance:

WO 93/00327, Astra Aktiebolag, which discloses the combination of a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH and an

acid degradable antibacterial compound. The proposed combination is especially suitable for the treatment of *H. pylori* infections.

WO 92/03135, Smithkline & French Laboratories, which discloses a combination of a
5 benzimidazole and an anti-*Helicobacter* agent, i.e. for instance pantoprazole in combination with amoxicillin and/or metronidazole.

In these proposed combination therapies each single active substance is administered separately in different dosage forms, each one comprising only one single active substance.
10 It is well known that patient compliance is a main factor in receiving a good result in medical treatments, especially in the treatment of *H. pylori* infections. Administration of two, three or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more different active substances combined in one fixed unit
15 dosage form, preferably a tablet.

It is well known that proton pump inhibitors are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, it is obvious that one of the active substances being a proton pump inhibitor must be protected from contact
20 with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of omeprazole as well as other proton pump inhibitors described in the prior art, see for example US-A 4,786,505 (AB Hässle).

There are problems to produce a fixed unit dosage form comprising a rather high amount of
25 active substances. Different active substances in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets containing acid susceptible proton pump inhibitors as active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be

destroyed upon administration by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

Summary of the invention

5

The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, enteric coating layered tablets, multilayered tablets or a capsule filled with more than one pharmaceutically active compound. The active compounds present are preferably an acid susceptible proton pump inhibitor and one or more antibacterial substances. These new dosage forms will simplify the regimen and improve the patient compliance.

10

Description of the Figures

- 15 Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with an antibacterial granulation (2). The tablet is covered by an overcoating layer (7).
- 20 Fig. 2 illustrates a cross-section of a tablet with two separate layers, one layer comprises enteric coating layered pellets of an acid susceptible proton pump inhibitor (1) in admixture with excipients (3) and the other layer comprises the antibacterial compound(s) (2). The tablet is covered by an overcoating layer (7).
- 25 Fig. 3 illustrates a cross-section of an enteric coating layered tablet comprising an acid susceptible proton pump inhibitor in admixture with one or more antibacterial substances (4). The tablet is covered by an enteric coating layer (7).

Fig. 4 illustrates an enteric coating layered tablet consisting of two separate layers, one layer comprises an acid susceptible proton pump inhibitor (5) and the other layer comprises the antibacterial compound(s) (6).

5 Detailed description of the invention

One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units together with one or more antibacterial compounds in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability during long-term storage to the active substances.

15 Alternatively, the prepared tablet has separate layers, one layer is in the form of compressed enteric coated layered units comprising the proton pump inhibitor and another layer comprises the antibacterial compound(s).

The new fixed dosage form is preferably in the form of a multiple unit tableted dosage form comprising enteric coating layered units of the one of the active substance which is acid susceptible, i.e. the proton pump inhibitor, and granules of the other active substance(s), i.e. the antibacterial granulation, as shown in Figs. 1 and 2. Alternatively, the different active compounds may be intimately mixed with each other and compressed into a conventional tablet, which is enteric coated as shown in Figs. 3 and 4. As a further alternative, the different active substances are dry mixed and filled into a capsule. In the latter preparation the acid susceptible proton pump inhibitor is in the form of enteric coating layered units (1).

Another object of the invention is to provide a tablet preparation comprising an acid susceptible proton pump inhibitor in admixture with one or more antibacterial substances compressed into a tablet, which tablet is enteric coating layered. Optionally a separating layer is applied before the tablet is enteric coating layered. Alternatively, the prepared
5 tablet core has separate layers, each one comprising different active substances. One of the layers comprises the acid susceptible proton pump inhibitor and another layer(s) comprises(-e) the antibacterial substance or substances, respectively. The prepared tablet is thereafter enteric coating layered.

10 A further object of the invention is to provide a dosage form which is divisible, such as divisible tablets.

Still a further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. The multiple unit tableted dosage form may be
15 dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

Furthermore, the present invention provides a capsule preparation comprising the acid
20 susceptible proton pump inhibitor in the form of enteric coating layered pellets mixed with one or more antibacterial compounds in the form of granules or pellets.

The antibacterial components may be formulated in the form of instant release, sustained release or extended release formulations. Alternatively, the components may be formulated
25 in an effervescent formulation.

The new fixed unit dosage forms comprise as active substances an acid susceptible proton pump inhibitor and one or more antibacterial compounds. The different active components used in the dosage forms are defined below.

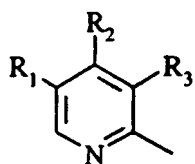
Active substances

The proton pump inhibitors are for example compounds of the general formula I



wherein

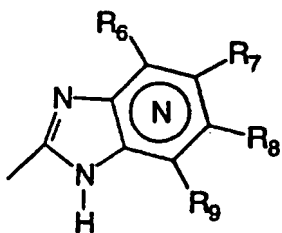
Het₁ is



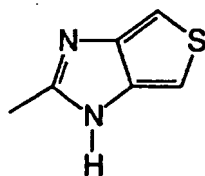
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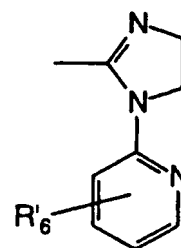
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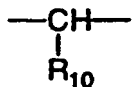
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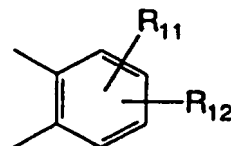
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R_1 , R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

5 R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6 is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

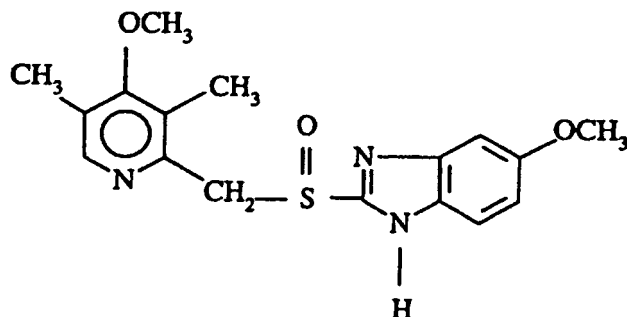
10 R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6 - R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

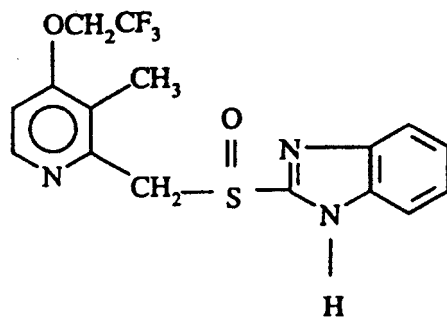
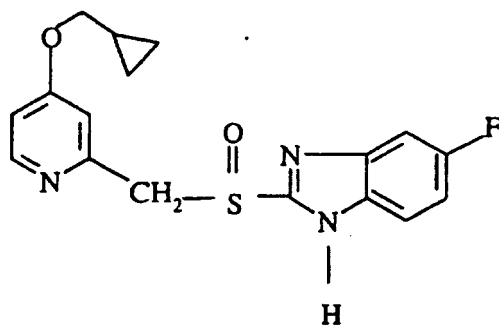
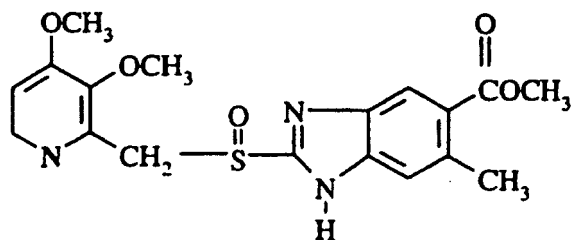
15 R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl and alkyl groups, alkoxy groups and moieties thereof may be branched and straight C_1 - C_9 -chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

Examples of proton pump inhibitors according to formula I are

20

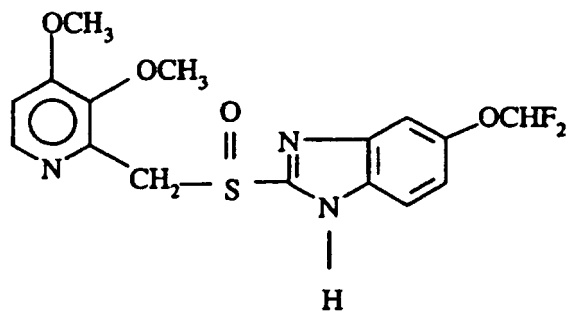


Omeprazole

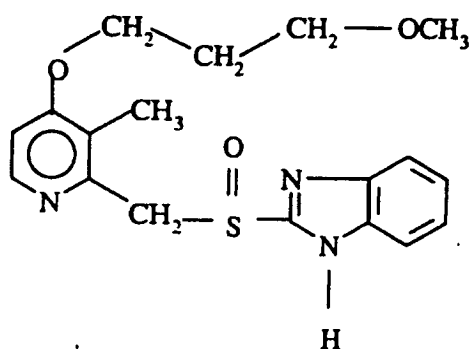


Lansoprazole

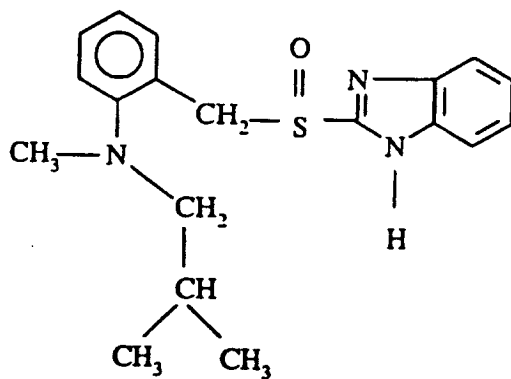
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Pantoprazole

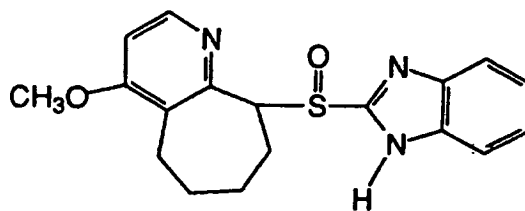
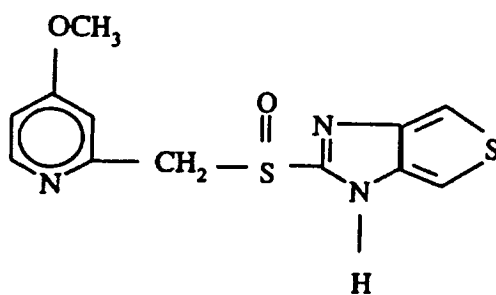


Pariprazole



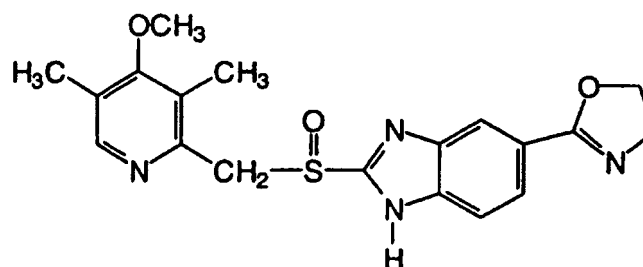
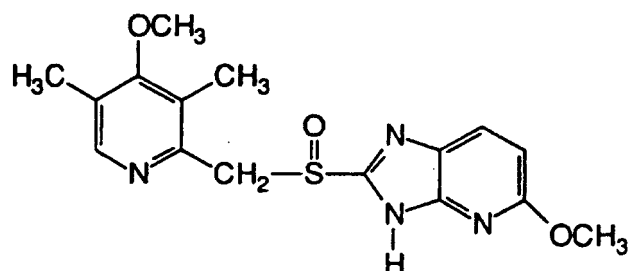
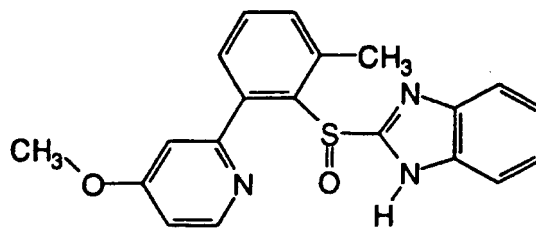
Leminoprazole

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The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO94/27988.

15

A wide variety of antibacterial compounds may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such antibacterial compounds include for example nitroimidazole antibiotics, tetracyclines, penicillins, cephalosporins, carbopenems, aminoglycosides, macrolide antibiotics, lincosamide antibiotics, 4-quinolones, rifamycins and nitrofurantoin. In the following examples of such antibacterial compounds are listed: ampicillin, amoxicillin, benzylpenicillin, phenoxymethylpenicillin, bacampicillin, pivampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin, methicillin, oxacillin, piperacillin, ticarcillin, flucloxacillin, cefuroxime, cefetamet, cefetrame, cefixime, cefoxitin, ceftazidime, ceftizoxime, latamoxef, cefoperazone, ceftriaxone, cefsulodin, cefotaxime, cephalixin, cefaclor, cefadroxil, cefalothin, cefazolin, cefpodoxime, ceftibuten, aztreonam, tigemonam, erythromycin, dirithromycin, roxithromycin, azithromycin, clarithromycin, clindamycin, paldimycin, lincomycin, vancomycin, spectinomycin, tobramycin, paromomycin, metronidazole, tinidazole, ornidazole, amifloxacin, cinoxacin, ciprofloxacin, difloxacin, enoxacin, fleroxacin, norfloxacin, ofloxacin, temafloxacin, doxycycline, minocycline, tetracycline, chlortetracycline, oxytetracycline, methacycline, rolitetracyclin, nitrofurantoin, nalidixic acid, gentamicin, rifampicin, amikacin, netilmicin, imipenem, cilastatin, chloramphenicol, furazolidone, nifuroxazide, sulfadiazin, sulfametoxazol, bismuth subsalicylate, colloidal bismuth subcitrate, gramicidin, mecillinam, cloxiquine, chlorhexidine, dichlorobenzylalcohol, methyl-2-pentylphenol. The active antibacterial agents could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above listed drugs may be used, for example to minimize the risk for developing resistance. Preferable antibacterial compounds for the new fixed dosage form are clarithromycin, erythromycin, roxithromycin, azithromycin, amoxicillin, metronidazole, tinidazole and tetracycline. Clarithromycin and metronidazole alone or in combination are especially suitable.

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor in the form of a racemat, an alkaline salt or one of its single enantiomers and one or more antibacterial compounds, is characterized in the following way. Individually enteric coating

layered units (small beads, granules or pellets) containing the acid susceptible proton pump inhibitor and optionally containing alkaline reacting substances, are mixed with the antibacterial compound(s) and conventional tablet excipients. Preferably, the antibacterial compound(s) and tablet excipients are in the form of a granulation. The dry mixture of
5 enteric coating layered units, antibacterial granulation and optionally excipients are compressed into the multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the proton pump inhibitor.

10 The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid
15 resistance does not decrease more than 10% during the compression of the pellets into tablets.

The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative to
20 that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid
25 Chromatography (HPLC).

Further specific components used in the fixed unit dosage forms of the present invention are defined below.

Core material - for enteric coating layered pellets comprising a proton pump inhibitor

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the acid susceptible proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

The seeds which are to be layered with the acid susceptible proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example are celluloses such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl-cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), sugar or starch or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing

conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

5

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives.

10

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak
15 inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as
20 trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

25

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets, the pellets may optionally be covered with one or more separating layer(s)
30 comprising pharmaceutical excipients optionally including alkaline compounds such as

pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s).

The separating layer(s) can be applied to the core material by coating or layering
5 procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone,
10 polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, water soluble salts of enteric coating polymers and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be
15 included into the separating layer(s).

When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and
20 may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$,
25 $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other
30 compounds may be added to increase the thickness of the layer(s) and thereby strengthen

the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

5

Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material and an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a water soluble salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in
10 the position to form a salt.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic
15 solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

20

The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other
25 plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness
30 of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so

that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers
5 e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

10 To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating is normally only limited by processing conditions.

15 Alternatively the enteric coating layer described above may be used for enteric coating layering of conventional tablets comprising a composition of an acid susceptible proton pump inhibitor and one or more antibacterial compounds, optionally covered by one of the separating layers described above. As a further alternative, the proton pump inhibitor may
20 be replaced in such a tablet by another gastric acid suppressing agents, such as a H_2 -receptor antagonist, for instance ranitidine, cimetidine or famotidine.

Over-coating layer

25 Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among
30 pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol,

polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further it may protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

10

The above described over-coating layer may also be used as a tablet coating layer to obtain tablets of good appearance.

Antibacterial granulation

15

The active substance in the form of one or more antibacterial compounds is dry mixed with inactive excipients and the mixture is wet massed with a granulation liquid. The wet mass is dried preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients for the antibacterial granulation are for instance, sodium starch glycolate, corn starch, crosslinked polyvinyl pyrrolidone, low substituted hydroxypropyl cellulose, microcrystalline cellulose and colloidal silicon dioxide anhydrous (Aerosil®). The dry mixture comprising antibacterial compound(s) is mixed with a suitable granulation liquid comprising for instance, polyvinyl pyrrolidone, hydroxypropyl cellulose, and optionally wetting agents, such as sodium lauryl sulphate, dissolved in purified water. Suitable lubricants for the tableting process are for instance, sodium stearyl fumarate, magnesium stearate and talc.

25

Multiple unit tablets

30

The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the granules comprising antibacterial compounds and tablet excipients. The dry mixture is compressed into a multiple unit tableted dosage form. The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further
5 enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives such as anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

The enteric coated pellets with or without an over-coat and the antibacterial granulation are
10 mixed with tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives and compressed into tablets.

The amount of enteric coating layered pellets constitutes less than 75 % by weight of the total tablet weight and preferably less than 60 %. By choosing small enteric coating layered
15 pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy. Larger amount of the granulation comprising the antibacterial compound(s) may reduce the amount of enteric coating layered pellets in the multiple unit tableted dosage form.

20

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of an acid susceptible proton pump inhibitor, optionally mixed with alkaline reacting compound(s), compressed into tablet together with a granulation containing antibacterial compound(s) and optionally tablet
25 excipients. The addition of an alkaline reacting material to the proton pump inhibitor is not necessary, in any sense but such a substance may further enhance the stability of the proton pump inhibitor or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating layer. The enteric coating layer(s) is making the pellets of the dosage form insoluble in acidic media, but disintegrating/dissolving in
30 near neutral to alkaline media such as, for instance the liquids present in the proximal part

of the small intestine, where dissolution of the proton pump inhibitor is desired. The antibacterial substance(s) may be released in the stomach. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the tablet and they may also contain one or more separating layer(s) optionally containing
5 alkaline substance(s).

Process

The process for the manufacture of the dosage form represents a further aspect of the
10 invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and then with the enteric coating layer(s) or a separating layer is spontaneously developed in situ between an alkaline core material and the enteric coating layer material. The coating
15 is carried out as described above and in the accompanying examples. The preparation of the granulation comprising the antibacterial compound(s) is also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

The enteric coating layered pellets, with or without an over-coat, are mixed with the
20 prepared granules, tablet excipients and other pharmaceutical acceptable additives and compressed into tablets. The tablet may be in the form of a two layer tablet, wherein one layer comprises the enteric coating layered pellets optionally mixed with inactive excipients and the other layer comprises the prepared granules of the antibacterial substance(s). Alternatively, the different active substances in the form of powders may be
25 intimately dry mixed with tablet excipients, wet massed and compressed into conventional tablets before applying an optional separating layer and an enteric coating layer. The tablet may be in the form of a two layer enteric coating layered tablet, wherein one layer comprises one of the active substances and the other layer comprises the other active substance(s). As a further alternative, the proton pump inhibitor in the form of enteric

coating layered pellets may be filled in a capsule together with the antibacterial substance(s) in the form of a granulation optionally mixed with pharmaceutical excipients.

Use of the preparation

5

The dosage forms according to the invention are especially advantageous in the treatment of *H. pylori* infections. They are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0,1-200 mg of the proton pump inhibitor and 0,1 mg - 1,2 g of the antibacterial compound(s). Preferably, each dosage form will comprise 10-80 mg of the proton pump inhibitor and 100-900 mg of the antibacterial compound(s), and more preferably 20-40 mg of proton pump inhibitor and 250-650 mg of the antibacterial compound(s), respectively.

15

The multiple unit tablet preparation is also suitable for dispersion in an aqueous liquid with neutral or slightly acidic pH-value before being orally administered or fed through a nasogastric tube.

20 The invention is illustrated more in detail in the following examples.

Examples

Example 1:

25

Multiple unit dosage form comprising omeprazole and metronidazole (batch size 10.000 tablets).

Core material

30 Magnesium omeprazole

12.00 kg

	Sugar sphere seeds	12.00 kg
	Hydroxypropyl methylcellulose	1.8 kg
	Water purified	35.4 kg
5	<u>Separating layer</u>	
	Core material (acc. to above)	23.50 kg
	Hydroxypropyl cellulose	2.35 kg
	Talc	4.03 kg
	Magnesium stearate	0.34 kg
10	Water purified	48.00 kg
	<u>Enteric coating layer</u>	
	Pellets covered with separating layer (acc. to above)	29.00 kg
	Methacrylic acid copolymer (30% suspension)	38.70 kg
15	Triethyl citrate	3.48 kg
	Mono- and diglycerides (NF)	0.58 kg
	Polysorbate 80	0.06 kg
	Water purified	22.68 kg
20	<u>Over-coating layer</u>	
	Enteric coating layered pellets (acc. to above)	44.7 kg
	Hydroxypropyl methylcellulose	0.58 kg
	Water purified	11.6 kg
25	<u>Tablets</u>	
	Prepared pellets comprising omeprazole as prepared above	933 g
	Metronidazole	4000 g
	Sodium starch glycolate	500 g
	Aerosil®	25 g
30	Sodium lauryl sulphate	20 g

	Polyvidone K90	253.1 g
	Microcrystalline cellulose	1181 g
	Water purified	2278 g
	Sodium stearyl fumarate	66.5 g
5	<u>Tablet coating solution (for 10 kg tablets)</u>	
	Hydroxypropyl methylcellulose	250 g
	Polyethylene glycol 6000	62.5 g
	Titanium dioxide	62.5 g
10	Water purified	2125 g
	Hydrogen pyroxide	0.75 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

15 The size of sugar sphere seeds are in the range of 0.25 to 0.35 mm.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl

20 citrate and polysorbate is sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets are coated with hydroxypropyl methylcellulose solution. The over-coating layered pellets are classified by sieving.

25 Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Metronidazole, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steamoven at 50°C. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

The enteric coating layered pellets with an over-coating layer, prepared granules, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x17 mm oval punches. The amount of omeprazole in each tablet is approx. 20 mg and the amount of metronidazole is approx. 400 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 20 kN. Tablet hardness measured is 150-164N.

The obtained tablets are covered with a conventional tablet coating layer.

10 Example 2:

Multiple unit dosage form comprising omeprazole and clarithromycin (batch size 10.000 tablets).

15 Tablets

Enteric coating layered pellets with an over-coating layer (manufacturing and composition as in example 1)	978 g
Clarithromycin	2500 g
Microcrystalline cellulose	3000 g
20 Sodium starch glycolate	350 g
Aerosil®	40 g
Sodium lauryl sulphate	12.5 g
Polyvidone K90	384.8 g
Water purified	3463 g
25 Magnesium stearate	105 g

Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
30 Titanium dioxide	62.5 g

Water purified	2125 g
Hydrogen pyroxide	0.75 g

Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Clarithromycin, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

The enteric coating layered pellets with an over-coating layer, prepared granules and magnesium stearate are mixed and compressed into tablets as in example 1. The amount of omeprazole in each tablet is approx. 20 mg and the amount of clarithromycin is approx. 250 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 14kN. Tablet hardness measured is 178-189N.

The obtained tablets are covered with a conventional tablet coating layer.

Example 3:

Multiple unit dosage form comprising omeprazole and clarithromycin (batch size 10.000 tablets).

Tablets

Enteric coating layered pellets with an over-coating layer	978 g
(manufacturing and composition as in example 1)	
Clarithromycin	5000 g
Microcrystalline cellulose	2500 g
Sodium starch glycolate	350 g
Aerosil®	40 g
Sodium lauryl sulphate	25 g

	Polyvidone K90	361.9 g
	Water purified	3257 g
	Magnesium stearate	91.7 g
5	<u>Tablet coating solution (for 10 kg tablets)</u>	
	Hydroxypropyl methylcellulose	250 g
	Polyethylene glycol 6000	62.5 g
	Titanium dioxide	62.5 g
	Water purified	2125 g
10	Hydrogen pyroxide	0.75 g

The antibacterial granulation is manufactured as in example 2. Enteric coating layered pellets with an over-coating layer, prepared granules and magnesium stearate are mixed and compressed into tablets using a rotary tableting machine equipped with 10x21 mm oval punches. The amount of omeprazole in each tablet is approx. 20 mg and the amount of clarithromycin is approx. 500 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 20kN. Tablet hardness measured is 105-128N.

The obtained tablets are covered with a conventional tablet coating layer.

20

Example 4:

Multiple unit dosage form comprising, metronidazole and clarithromycin (batch size 2.500 tablets).

25

Core material

	Magnesium omeprazole	15.00 kg
	Sugar sphere seeds	15.00 kg
	Hydroxypropyl methylcellulose	2.25 kg
30	Water purified	40.25 kg

Separating layer

	Core material (acc. to above)	15.00 kg
	Hydroxypropyl cellulose	1.5 kg
5	Talc	2.57 kg
	Magnesium stearate	0.21 kg
	Water purified	30.00 kg

Enteric coating layer

10	Pellets covered with separating layer (acc. to above)	18.00 kg
	Methacrylic acid copolymer (30% suspension)	30.00 kg
	Triethyl citrate	2.7 kg
	Mono- and diglycerides (NF)	0.49 kg
	Polysorbate 80	0.05 kg
15	Water purified	19.00 kg

Tablets

	Enteric coating layered pellets (acc. to above)	246 g
	Clarithromycin	625 g
20	Metronidazole	1000 g
	Microcrystalline cellulose	375 g
	Sodium starch glycolate	125 g
	Aerosil®	10 g
	Sodium lauryl sulphate	8 g
25	Polyvidone K90	117.8 g
	Water purified	1060 g
	Sodium stearyl fumarate	48.2 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is
30 sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate is sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets are classified by sieving.

Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Clarithromycin, metronidazole, microcrystalline cellulose, sodium starch glycolate and Aerosil are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

Enteric coating layered pellets, prepared granules and sodium stearyl fumarate are mixed and compressed into tablets as in example 3. The amount of omeprazole in each tablet is approx. 20 mg, the amount of metronidazole is 400 mg and the amount of clarithromycin is 250 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 24 kN. Tablet hardness measured is 130-142N.

Example 5:

Multiple unit dosage form comprising lansoprazole and clarithromycin (batch size 1.000 tablets).

Core material

Lansoprazole	400 g
Sugar sphere seeds	400 g
Hydroxypropyl methylcellulose	80 g
Water purified	1200 g

Separating layer

	Core material (acc. to above)	400 g
	Hydroxypropyl cellulose	40 g
	Talc	69 g
5	Magnesium stearate	6 g
	Water purified	800 g

Enteric coating layer

	Pellets covered with a separating layer (acc. to above)	400 g
10	Methacrylic acid copolymer (30% suspension)	667 g
	Triethyl citrate	60 g
	Mono- and diglycerides (NF)	10 g
	Polysorbate 80	1 g
	Water purified	391 g

15

Tablets

	Enteric coating layered pellets (acc. to above)	89.8 g
	Clarithromycin	250 g
	Microcrystalline cellulose	300 g
20	Sodium starch glycolate	35 g
	Aerosil®	4 g
	Sodium lauryl sulphate	1.25 g
	Polyvidone K90	45.2 g
	Water purified	406.8 g
25	Magnesium stearate	10.1 g

Suspension layering is performed in a fluid bed apparatus. Lansoprazole is sprayed onto the sugar sphere seeds from a suspension containing the dissolved binder in a water solution.

Pellets covered with separating layer and enteric coating layer are produced as in example

30 1. The antibacterial granulation is manufactured as in example 2.

Enteric coating layered pellets, prepared granules and magnesium stearate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x17 mm oval punches. The amount of lansoprazole in each tablet is approx. 20 mg and the amount of clarithromycin is approx. 250 mg. The upper punch force is set to 5.8 kN , and the tablet hardness is measured 63N.

Example 6.

- 10 Multiple unit dosage form comprising (s)-omeprazole magnesium salt, metronidazole and clarithromycin (batch size 200 tablets).

Core material

	(s)-Omeprazole magnesium salt	120 g
15	Sugar sphere seeds	150 g
	Hydroxypropyl methylcellulose	18 g
	Polysorbate 80	2.4 g
	Water purified	562 g

20 Separating layer

	Core material (acc. to above)	200 g
	Hydroxypropyl cellulose	30 g
	Talc	51.4 g
	Magnesium stearate	4.3 g
25	Water purified	600 g

Enteric coating layer

	Pellets covered with separating layer (acc. to above)	250 g
	Methacrylic acid copolymer (30% suspension)	333.7 g
30	Triethyl citrate	30 g

	Mono- and diglycerides (NF)	5 g
	Polysorbate 80	0.5 g
	Water purified	196 g
5	<u>Metronidazole and clarithromycin granulation</u>	
	Clarithromycin	3500 g
	Metronidazole	5600 g
	Microcrystalline cellulose	1400 g
	Sodium starch glycolate	700 g
10	Aerosil®	56 g
	Polyvidon K90	511 g
	Water purified	4600 g
	<u>Tablets</u>	
15	Pellets comprising (s)-omeprazole Mg-salt (acc. to above)	25.5 g
	Granulation comprising clarithromycin and metronidazole (acc. to above)	168.1 g
	Microcrystalline cellulose	40 g
	Sodium stearyl fumarate	4.7 g
20	<u>Tablet coating solution (for 10kg tablets)</u>	
	Hydroxypropyl methylcellulose	250 g
	Polyethylene glycol 6000	62.5 g
	Titanium dioxide	62.5 g
25	Water purified	2125 g
	Hydrogen pyroxide	0.75 g

Suspension layering is performed in a fluid bed apparatus. (s)-Omeprazole magnesium salt is sprayed onto sugar sphere seedes from a water suspension containing the dissolved

binder and polysorbate 80. The size of sugar sphere seeds are in the range of 0.25 to 0.35 mm.

The prepared core material is covered with a separating layer in a fluid bed apparatus with
5 hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate is sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets are classified by sieving.

10 Polyvidone K90 is dissolved in purified water to form the granulation liquid. Clarithromycin, metronidazole, microcrystalline cellulose, sodium starch glycolate and Aerosil[®] are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1mm in an oscillating mill equipment.

15 The enteric coating layered pellets, prepared granules, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets on a tableting machine equipped with 10x21 mm oval punches. The amount of (s)-omeprazole is approx. 20 mg, the amount of metronidazole is approx. 400 mg and the amount of clarithromycin is approx. 250 mg. Tablet hardness tested with a Schleuniger apparatus was 140-150N.

20

The obtained tablets are covered with a conventional tablet coating layer.

The results from tests on acid resistance of the compressed tablets are disclosed in Table 1, below.

25

Table 1

Example No	Acid resistance, tablets (%), n=3
------------	--------------------------------------

30

1

95

	2	99
	3	91
	4	92
	5	90
5	6	93

Example 7:

An enteric coating layered tablet comprising magnesium omeprazole, clarithromycin and
10 metronidazol (batch size 1.000 tablets).

Tablets

	Magnesium omeprazole	20 g
	Clarithromycin	250 g
15	Metronidazole	400 g
	Microcrystalline cellulose	150 g
	Sodium starch glycolate	50 g
	Aerosil®	4 g
	Sodium lauryl sulphate	3.2 g
20	Polyvidone K90	50 g
	Water purified	450 g
	Sodium stearyl fumarate	18 g

Solution for separating layer (for 10 kg tablets)

25	Hydroxypropyl methylcellulose	300 g
	Hydrogen peroxide (30%)	0.003 g
	Water purified	2700 g

Solution for enteric coating layer (for 10 kg tablets)

30	Methacrylic acid copolymer dispersion (30%)	2450 g
----	---	--------

Polyethylene glycol 400	80 g
Titanium dioxide	100 g
Water purified	1960 g

- 5 Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Magnesium omeprazole, clarithromycin, metronidazole, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an
10 oscillating mill equipment.

The prepared granules and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x19 mm oval punches. The amount of omeprazole in each tablet is 20 mg, the amount of clarithromycin is 250 mg and the
15 amount of metronidazole is 400 mg.

The obtained tablets are covered with a separating layer and an enteric tablet coating layer.

Example 8:

20

An enteric coating layered tablet comprising lansoprazole and clarithromycin (batch size 1.000 tablets).

Tablets

25	Lansoprazole	20 g
	Clarithromycin	250 g
	Microcrystalline cellulose	150 g
	Sodium starch glycolate	50 g
	Aerosil®	4 g
30	Sodium lauryl sulphate	3.2 g

Polyvidone K90	50 g
Water purified	450 g
Sodium stearyl fumarate	18 g

5 Solution for separating layer (for 10kg tablets)

Hydroxypropyl methylcellulose	300 g
Hydrogen peroxide (30%)	0.003 g
Water purified	2700 g

10 Solution for enteric coating layer (for 10 kg tablets)

Methacrylic acid copolymer dispersion (30%)	2450 g
Polyethylene glycol 400	80 g
Titanium dioxide	100 g
Water purified	1960 g

15

Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Lansoprazole, clarithromycin, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

20

The prepared granules and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x19 mm oval punches. The amount of lansoprazole in each tablet is 20 mg, the amount of clarithromycin is 250 mg.

25

The obtained tablets are covered with a separating layer and an enteric tablet coating layer.

Example 9:

30 A capsule formulation comprising omeprazole and metronidazol.

Core material

	Magnesium omeprazole	10.00 kg
	Sugar sphere seeds	10.00 kg
5	Hydroxypropyl methylcellulose	1.5 kg
	Water purified	29.65 kg

Separating layer

	Core material (acc. to above)	20.00 kg
10	Hydroxypropyl cellulose	2.00 kg
	Talc	3.43 kg
	Magnesium stearate	0.29 kg
	Water purified	40.00 kg

15 Enteric coating layer

	Pellets covered with a separating layer (acc. to above)	24.00 kg
	Methacrylic acid copolymer (30% suspension)	40.00 kg
	Triethyl citrate	3.6 kg
	Mono- and diglycerides (NF)	0.6 kg
20	Polysorbate 80	0.06 kg
	Water purified	24.45 kg

Metronidazole granulation

	Metronidazole	5000 g
25	Polyvidone K90	62.6 g
	Water purified	562.9 g

Polyvidon K90 is dissolved in purified water to form the granulation liquid. The liquid is added to metronidazole and the mass is wet-mixed. The wet mass is dried in a steam oven.

30 The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

Capsules

	Metronidazole granulation (acc. to above)	1250.8 g
	Enteric coating layered pellets (acc. to above)	104 mg/capsule
5	(manufacturing as in Example 4)	
	Magnesium stearate	24.8 g

The metronidazole granulation is mixed with magnesium stearate. Prepared granules and enteric coating layered pellets are filled into capsules, size 0, using a capsule filling
10 machine equipped with powder dosing unit and pellet filler. The amount of omeprazole in each capsule is 20 mg and the amount of metronidazole is 400 mg. Capsule filling speed is set to 61 rpm.

Example 10:

15

A capsule formulation comprising omeprazole and clarithromycin.

Core material

	Magnesium omeprazole	15.00 kg
20	Sugar sphere seeds	15.00 kg
	Hydroxypropyl methylcellulose	2.25 kg
	Water purified	44.00 kg

Separating layer

25	Core material (acc. to above)	30.00 kg
	Hydroxypropyl cellulose	3.00 kg
	Talc	5.14 kg
	Magnesium stearate	0.43 kg
	Water purified	60.00 kg

30

Enteric coating layer

	Pellets covered with a separating layer (acc. to above)	750 g
	Methacrylic acid copolymer	322.5 g
	Triethyl citrate	96.8 g
5	Mono- and diglycerides (NF)	16.1 g
	Polysorbate 80	1.61 g
	Water purified	631.4 g

Over-coating layer

10	Hydroxypropyl methylcellulose	22.5 g
	Water purified	427.5 g

Clarithromycin granulation

	Clarithromycin	5000 g
15	Ethanol (99.5%)	2064 g
	Sodium lauryl sulphate	50 g

Sodium lauryl sulphate is dissolved in ethanol to form the granulation liquid. The liquid is added to clarithromycin and the mass is wet-mixed. The wet mass is dried in a steam oven.

20 The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

Capsules

	Clarithromycin granulation (acc. to above)	1500 g
	Hydroxypropyl cellulose (L-HPC)	75 g
25	Magnesium stearate	31.5 g
	Pellets covered with an overcoating layer (acc. to above and manufacturing as in example 1)	96.7 mg/capsule

The clarithromycin granulation is mixed with L-HPC and magnesium stearate and capsules of size 00 is filled as in example 8. The amount of omeprazole in each capsule is 20 mg and the amount of clarithromycin is 500 mg.

5 Example 11:

A capsule formulation comprising omeprazole, clarithromycin and metronidazole.

Capsules

10	Clarithromycin granulation	1805 g
	(manufacturing and composition as in example 9)	
	Hydroxypropyl cellulose (L-HPC)	90.3 g
	Metronidazole	2670 g
	Magnesium stearate	91.3 g
15	Pellets covered with an overcoating layer	96.7 mg/capsule
	(manufacturing and composition as example 1)	

The clarithromycin granulation is mixed with metronidazole, L-HPC and magnesium stearate. Capsules of size 00 is filled as in example 8. The amount of omeprazole in each capsule is 20 mg, the amount of metronidazole is 400 mg and the amount of clarithromycin is 250 mg.

Example 12:

25 A dosage form comprising lansoprazole and clarithromycin, filled into capsules in the form of granules.

Core material

	Lansoprazole	400 g
	Sugar sphere seeds	400 g
30	Hydroxypropyl methylcellulose	80 g

Water purified 1200 g

Separating layer

Core material (acc. to above) 400 g

5 Hydroxypropyl cellulose 40 g

Talc 69 g

Magnesium stearate 6 g

Water purified 800 g

10 Enteric coating layer

Pellets covered with separating layer (acc. to above) 400g

Methacrylic acid copolymer (30% suspension) 667 g

Triethyl citrate 60 g

Mono- and diglycerides (NF) 10 g

15 Polysorbate 80 1 g

Water purified 391 g

Clarithromycin granulation

Clarithromycin 5000 g

20 Ethanol (99.5%) 2064 g

Sodium lauryl sulphate 50 g

Sodium lauryl sulphate is dissolved in ethanol to form the granulation liquid. The liquid is added to clarithromycin and the mass is wet-mixed. The wet mass is dried in a steam oven.

25 The prepared granulation is milled through sieve 1mm in an oscillating mill equipment.

Capsules

Clarithromycin granulation (acc. to above) 1500 g

Hydroxypropyl cellulose (L-HPC) 75 g

30 Magnesium stearate 31.5 g

Enteric coating layered pellets (acc. to above and 94 mg/capsule
manufacturing as in example 5)

The clarithromycin granulation is mixed with L-HPC and magnesium stearate and capsules
5 of size 00 is filled as in example 8. The amount of lansoprazole in each capsule is 20 mg
and the amount of clarithromycin is 500 mg.

The best mode to carry out the invention are dosage forms of the compositions described in
Examples 3, 4 and 6.

10

The enteric coating layered pellets and other intermediate products used in the
compositions described above, may also be prepared as described in the following
examples.

15 Example 13

Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material

20	Magnesium omeprazole	600 g
	Mannitol	1000 g
	Microcrystalline cellulose	300 g
	Hydroxypropyl cellulose	100 g
	Sodium lauryl sulphate	6 g
25	Water purified	802 g

Separating layer

	Core material (acc. to above)	400 g
	Hydroxypropyl methylcellulose	48 g
30	Water purified	960 g

Enteric coating layer

- | | | |
|---|---|-------|
| | Pellets covered with separating layer (acc. to above) | 200 g |
| | Methacrylic acid copolymer | 100 g |
| 5 | Triethyl citrate | 30 g |
| | Mono- and diglycerides (NF) | 5 g |
| | Polysorbate 80 | 0.5 g |
| | Water purified | 309 g |
- 10 Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid. Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.
- 15 The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.
- 20 The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layering.

Example 15

5

Preparation of enteric coating layered pellets with silicon dioxide seeds.

Core material

	Magnesium omeprazole	8.00 kg
10	Silicon dioxide	8.00 kg
	Hydroxypropyl methylcellulose	1.41 kg
	Sodium lauryl sulphate	0.08 kg
	Water purified	28.00 kg

15 Separating layer

	Core material (acc. to above)	10.00 kg
	Hydroxypropyl methylcellulose	0.80 kg
	Water purified	10.00 kg

20 Enteric coating layer

	Pellets covered with separating layer (acc. to above)	300 g
	Methacrylic acid copolymer	124 g
	Polyethylene glycol 400	25 g
	Mono- and diglycerides (NF)	3 g
25	Polysorbate 80	1 g
	Water purified	463 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved
30 binder and a surface active ingredient.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

Example 16

Preparation of enteric coating layered pellets.

10

Enteric coating layer

Pellets covered with separating layer

(manufacturing and composition

as in example 13)

500 g

15 Methacrylic acid copolymer

250 g

Polyethylene glycol 6000

75 g

Mono- and diglycerides (NF)

12.5 g

Polysorbate 80

1.2 g

Water purified

490 g

20

Example 17

Preparation of enteric coating layered pellets.

25 Enteric coating

Pellets covered with separating layer

500 g

(manufacturing and composition as in example 1)

Hydroxypropyl methylcellulose phthalate

250 g

Cetanol

50 g

30 Ethanol (95%)

1000 g

Acetone	2500 g
---------	--------

Example 18

5 Preparation of enteric coating layered pellets.

Core material

	Omeprazole	225 g
	Mannitol	1425 g
10	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
	Lactose anhydrous	80 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate dihydrate	8 g
15	Water purified	350 g

Separating layer

	Core material (acc. to above)	300 g
	Hydroxypropyl cellulose	30 g
20	Talc	51 g
	Magnesium stearate	4 g

Enteric coating layer

	Pellets covered with separating layer (acc. to above)	300 g
25	Methacrylic acid copolymer	140 g
	Triethyl citrate	42 g
	Mono- and diglycerides (NF)	7 g
	Polysorbate 80	0.7 g

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm. The prepared core material is covered with a separating layer and enteric coating layered as described in previous examples.

Preparation of active substance.

10

Magnesium omeprazole used in the examples is produced according to the process described in WO/SE94/00680, omeprazole is produced according to the process disclosed in EP-A1 0005129, and the single enantiomers of omeprazole salts are produced as described in WO/SE94/00509. These documents are hereby incorporated in a whole by reference.

15

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with at least one antibacterial compound and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components.
2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.
3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.
4. A dosage form according to claim 1, wherein the dosage form comprises an acid susceptible proton pump inhibitor and two antibacterial compounds.
5. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole or its single enantiomers or an alkaline salt thereof.
6. A dosage form according to claim 1, wherein the proton pump inhibitor is (s)-omeprazole magnesium salt.
7. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole.
8. A dosage form according to any of claims 5 - 7, wherein the antibacterial compound is clarithromycin and/or metronidazole.
9. A dosage form according to any of claims 5 - 7, wherein the antibacterial compound is amoxicillin and/or clarithromycin or metronidazole.

10. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-80 mg and the amount of antibacterial compound(s) is in the range of 100-900 mg.

5 11. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 20-40 mg and the amount of antibacterial compound(s) is in the range of 250-650 mg.

12. A tableted dosage form according to claim 2, wherein the dosage form consists of
10 two separate layers, each one comprising different active substance(s).

13. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the acid susceptible proton pump inhibitor in the form of individually enteric coating layered pellets compressed together with an
15 antibacterial granulation into a tablet, whereby the enteric coating layer covering the individual pellets has mechanical properties such that the tableting of the pellets together with the antibacterial granulation and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the individually enteric coating layered pellets.

20

14. A tableted dosage form according to claim 13, wherein the acid resistance of the individually enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

25 15. A tableted dosage form according to 13, wherein the acid resistance of the individually enteric coating layered pellets does not decrease more than 10 % during the compression of the individual pellets into the multiple unit tableted dosage form.

16. A tableted dosage form according to claim 13, wherein the enteric coating of the
30 individual pellets comprises a plasticized enteric coating layer material.

17. A tableted dosage form according to claim 13, wherein the individually enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.
- 5 18. A tableted dosage form according to claim 13, wherein the enteric coating layered pellets consist of a seed layered with the proton pump inhibitor.
19. A tableted dosage form according to claim 13, wherein the tablet is divisible.
- 10 20. A tableted dosage form according to claim 19, wherein the tablet is dispersible to a suspension of individually enteric coating layered pellets in an aqueous liquid.
21. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating
15 layered tablet, optionally with a separating layer under the enteric coating layer and the tablet comprises at least two different pharmaceutically active substances in admixture with each other.
22. A process for the manufacture of a fixed dosage form comprising an acid
20 susceptible proton pump inhibitor and one or more antibacterial compounds in a capsule, characterized in that the proton pump inhibitor is prepared in the form of individually enteric coating layered pellets and the pellets are filled into a capsule together with the antibacterial compound(s) optionally mixed with pharmaceutically acceptable excipients.
- 25 23. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor and one or more antibacterial compounds in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of individually enteric coating layered pellets and these pellets are mixed with a prepared antibacterial granulation and optionally pharmaceutically acceptable tablets
30 excipients whereafter the dry mixture is compressed into a multiple unit tablet without

giving any significant change of the acid resistance of the enteric coating layer covering the individually enteric coating layered pellets.

24. A process for the manufacture of a fixed dosage form comprising an acid
5 susceptible proton pump inhibitor and one or more antibacterial compound(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with the antibacterial compound(s) and pharmaceutically acceptable excipients whereafter the dry mixture is compressed into a tablet, which tablet is covered with an enteric coating layer and optionally a separating layer is applied onto the tablet before the enteric coating layer.
- 10 25. A dosage form according to any of claims 1 to 21 for use in the treatment of disorders associated with *Helicobacter* infections in mammals and man.
- 15 26. A dosage form according to claim 25, wherein the disorder is a gastric disorder associated with *Helicobacter pylori* infections.
- 20 27. A method for the treatment of disorders associated with *Helicobacter* infections in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 21.
28. A method according to claim 27, wherein the disorder is a gastric disorder associated with *Helicobacter pylori* infections.
- 25 29. Use of a dosage form according to any of claims 1 to 21 for the manufacture of a medicament for the treatment of disorders associated with *Helicobacter* infections in mammals and man.
30. Use of a dosage form according to claim 29, wherein the disorder is a gastric disorder associated with *Helicobacter pylori* infections.

Fig. 1

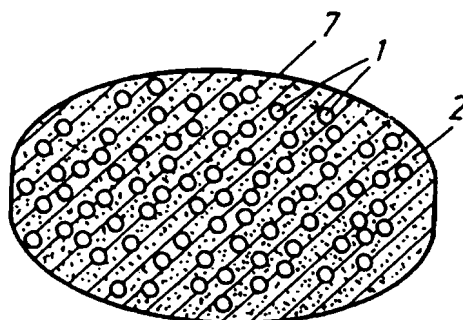


Fig. 2

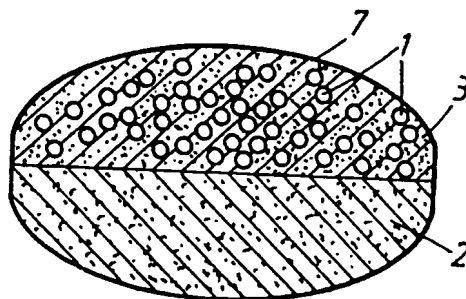


Fig. 3

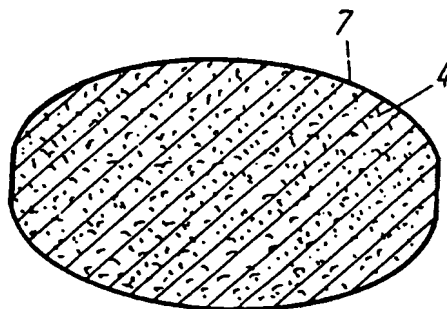
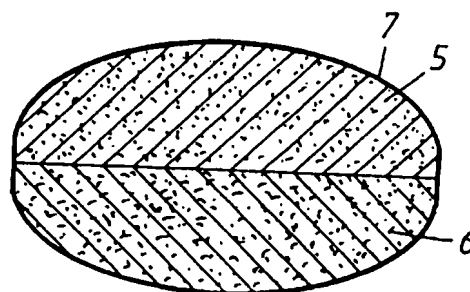


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/44, A61K 31/71, A61K 31/41, A61K 31/43, A61K 9/20, A61K 9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, USFULLTEXT, CLAIMS, EMBASE, MEDLINE, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0642797 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 15 March 1995 (15.03.95) --	1-26
Y	WO 9211849 A1 (THE PROCTER & GAMBLE COMPANY), 23 July 1992 (23.07.92), page 3, line 24 - line 32; page 7, line 22 - line 24 --	1-26
Y	Dialog Information Services, File 73, EMBASE, Dialog accession no. 9150953, EMBASE accession no. 94095444, Logan R.P.H. et al: "Eradication of Helicobacter pylori with clarithromycin and omeprazole", GUT (United Kingdom), 1994, 35/3 (323-326) --	1-26

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"O" document referring to an oral disclosure, use, exhibition or other means	
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Date of the actual completion of the international search

9 May 1996

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90) -- -----	1-26

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 27-30
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0642797	15/03/95	NONE	
WO-A1- 9211849	23/07/92	AU-A- 1252592 US-A- 5128140	17/08/92 07/07/92
EP-A1- 0365947	02/05/90	SE-T3- 0365947 AU-B,B- 612525 AU-A- 4365089 CA-A- 2000932 DE-T- 68907177 ES-T- 2055775 HK-A- 123394 IE-B- 62640 JP-A- 2164821 LV-B- 10382 PT-B- 92103 SE-A- 8803822 SG-A- 123894 US-A- 5178868	11/07/91 03/05/90 26/04/90 13/01/94 01/09/94 18/11/94 22/02/95 25/06/90 20/12/95 09/08/95 26/10/88 17/03/95 12/01/93

REFERENCES



FOR



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 45/06, 31/44, 31/19, 31/54, 9/26, 9/54	A1	(11) International Publication Number: WO 97/25064 (43) International Publication Date: 17 July 1997 (17.07.97)
(21) International Application Number: PCT/SE96/01735 (22) International Filing Date: 20 December 1996 (20.12.96) (30) Priority Data: 9600070-8 8 January 1996 (08.01.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): DEPUI, Helene [FR/SE]; Wrangelsgatan 7B, S-416 62 Göteborg (SE). LUNDBERG, Per, Johan [SE/SE]; Torsgatan 6, S-431 38 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A NSAID (57) Abstract <p>An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more NSAIDs in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer. The fixed formulation is in the form of an enteric coating layered tablet, a capsule or a multiple unit tableted dosage form. The multiple unit dosage forms are most preferred. The new fixed formulation is especially useful in the treatment of gastrointestinal side-effects associated with NSAID treatment.</p> <div data-bbox="901 1155 1396 1428" data-label="Image"> </div>		

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GA	Gabon			VN	Viet Nam

ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A NSAID

Field of the invention

5 The present invention is related to new oral pharmaceutical preparations especially for use in the treatment and prophylaxis of gastrointestinal disorders associated with the use of Non Steroidal Antiinflammatory Drugs (NSAIDs). The present preparations comprise an acid susceptible proton pump inhibitor in combination with one or more NSAID(s) in a new fixed unit dosage form, especially a tableted dosage form . Furthermore, the present
10 invention refers to a method for the manufacture of such preparations and the use of such preparations in medicine.

BACKGROUND OF THE INVENTION

15 NSAIDs including acetyl salicylic acid are among the most commonly prescribed and used drugs world-wide. Despite the therapeutic benefits of NSAIDs, their use is frequently limited by an increased risk of gastrointestinal side-effects, mainly upper gastrointestinal side-effects like peptic ulceration and dyspeptic symptoms.

20 The relative risk of developing a gastric ulcer during NSAID treatment is increased by a factor 40-50, and the relative risk of developing a duodenal ulcer is increased by a factor 8-10 (McCarty DM. Gastroenterology 1989;96:662). The relative risk of developing an ulcer complication like bleeding and perforation of the stomach is increased by a factor 1.5-5 (Hawkey C. BMJ 1990;300:278). Further, dyspeptic symptoms are experienced in 30-60%
25 of those on NSAID treatment (Larkai EN.AmJGas 1987;82:1153).

In the UK, NSAIDs account for 25% of all reports of adverse drug reactions received by the authorities, and the corresponding figure is 21% in USA. Therefore, therapies which avoid gastrointestinal side-effect caused by NSAIDs is requested.

Attempts to modify the NSAID structure in order to prevent such side-effects have so far been less successful. The most promising solution to the problem of healing and preventing NSAID associated upper gastrointestinal problems like ulcers and dyspeptic symptoms in patients with a need for continuous NSAID treatment is to combine the NSAID treatment with an anti-ulcer drug approved for the healing and/or prophylaxis of NSAID associated gastrointestinal side-effects such as prostaglandin analogues, H₂-receptor antagonists or proton pump inhibitors.

- Established risk factors for developing NSAID associated upper gastrointestinal side-effects and complications are for instance high age, previous peptic ulcer and/or bleeding, high dose of NSAID, co-therapy with steroids, and co-therapy with anticoagulants. This means, that for example fragile and elderly patients tolerating a complication like bleeding or perforation badly, should receive prophylactic treatment in connection with their NSAID treatment.

NSAIDs are mainly used for the treatment of chronic diseases like rheumatoid arthritis and osteoarthritis, which are most often seen in the elderly population. Compliance is especially important in elderly and fragile patients, who have the highest risk of developing a life-threatening complication to NSAID treatment like bleeding or perforation. It is known that 50% of all peptic ulcer deaths occur in NSAID users and that 68% of these are >75 years old (Catford:Health Trends 1986;18:38). This is confirmed in another study concluding, that NSAID-related deaths occur primarily in those > 75 years of age (Guess. J Clin Epidemiol 1988;41:35). The importance of compliance is further supported by the finding, that a majority of peptic ulcers associated with NSAID treatment are asymptomatic until the event.

Omeprazole being a well known proton pump inhibitor has been shown to be able to prevent gastric and duodenal erosions in healthy volunteers during treatment with acetyl salicylic acid. Clinical studies have shown, that omeprazole heals gastric as well as duodenal

ulcers as fast and effectively in patients on continuous NSAID treatment as in non-NSAID users (Walan A. N Engl J Med 1989;320:69). These results have been the basis for an amendment to the dose recommendation for the use of omeprazole in healing of gastric and duodenal ulcers during continuous NSAID treatment approved by regulatory authorities in
5 UK and Sweden.

Recent studies confirm, that omeprazole significantly reduces the risk of developing gastric ulcers, duodenal ulcers and also dyspeptic symptoms in patients on continuous NSAID treatment.

10

EP 0 426 479 describes tablet compositions comprising a NSAID such as ibuprofen and a gastric acid inhibiting drug, such as cimetidin etc. No specific arrangement is taken to avoid degradation if the gastric acid inhibitor is an acid susceptible compound, such as a proton pump inhibitor.

15

In proposed therapies comprising NSAID(s) and an acid susceptible proton pump inhibitor the different active substances are administered separately. It is well known that patient compliance is a main factor in receiving a good result in medical treatments. Therefore, administration of two or even more different tablets to the patient is not convenient or
20 satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more different active substances combined in one fixed unit dosage form, preferably a tablet.

Some anti-ulcer drugs such as proton pump inhibitors are susceptible to
25 degradation/transformation in acid reacting and neutral media as mentioned above. In respect of the stability properties, it is obvious that the one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of proton pump inhibitors described in the prior art, see for example US-A 4,786,505 (AB Hässle)
30 comprising omeprazole.

There are problems to produce a fixed unit dosage form comprising a rather high amount of active substance. Active substances with different physical properties combined in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises
5 specific problems when enteric coating layered pellets containing the acid susceptible proton pump inhibitor are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet, the susceptible active substance will be destroyed upon administration by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

10

Summary of the invention

The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, enteric coating layered tablets, multilayered tablets or capsules filled with
15 more than one pharmaceutically active compound. The active compounds are preferably an acid susceptible proton pump inhibitor in combination with one or more NSAIDs and wherein at least the proton pump inhibitor is protected by an enteric coated layer. These new dosage forms will simplify the regimen and improve the patient compliance.

20 Description of the Figures

Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with a fast disintegrating granulate comprising a NSAID (2). The tablet is
25 covered by an filmcoating layer (13).

Fig. 2 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) and a NSAID in the form of cyclodextrin complex (3) included in a fast disintegrating granulate
30 (4). The tablet is covered by a filmcoating layer (13).

Fig. 3 illustrates a cross-section of a tablet with two separate layers, one layer comprises an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with excipients (5) and the other layer comprises a NSAID (6) included in a gelling matrix giving extended release. The separate layers are optionally separated by a separating layer (12) and the tablet is covered by a filmcoating layer (13).

Fig. 4 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) and a NSAID in the form of enteric coating layered pellets (7) in admixture with excipients (5). The tablet is covered by a filmcoating layer (13).

Fig. 5 illustrates a cross-section of an enteric coating layered tablet comprising an acid susceptible proton pump inhibitor (8) in admixture with one or more NSAID(s) (9) and excipients (5). The tablet is covered by an enteric coating layer (11) and optionally a separating layer (10) is layered in between the tablet core and the enteric coating layer.

Fig. 6 illustrates a tablet comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with a fast disintegrating granulate (4) in a tablet core, surrounded by a coating layer comprising a NSAID substance/granulation (2). The tablet is covered by a pigmented filmcoating layer (13).

Detailed description of the invention

One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an anti-ulcer drug, preferably an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units, together with one or more NSAIDs and tablet excipients compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the

individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability to the active substances during long-term storage.

Alternatively, the prepared tablet has separate layers, one layer that comprises the acid susceptible proton pump inhibitor in the form of compressed enteric coated layered units and another layer that comprises the NSAID(s).

The new fixed dosage form is preferably in the form of a multiple unit tableted dosage form comprising enteric coating layered units of the acid susceptible substance and the other active substance(s) in the granulated material constituting the rest of the compressed tablet, as shown in Fig. 1.

Alternatively, the different active substances may be intimately mixed with each other and compressed into a conventional tablet, which is enteric coating layered, see Fig. 5, or both active substances are in the form of enteric coating layered pellets compressed into a multiple unit tableted formulation together with preferably fast disintegrating granules of inactive excipients, as exemplified in Fig. 4.

Further alternatives are exemplified as multiple unit dosage forms wherein the proton pump inhibitor is in the form of individually enteric coating layered units and the NSAID(s) in the form of a) a complex to obtain improved bioavailability, see Fig. 2, or b) in the form of a gelling matrix resulting in a preparation with extended release of the NSAID(s), see Fig. 3. A further alternative is a multiple dosage form with the proton pump inhibitor in the form of individually enteric coating layered units compressed into a tablet and thereupon a separate layer of the NSAID(s) is applied by spray layering on the tablet. The tablet is covered by a pigmented filmcoating layer to protect the NSAID(s), see Fig. 6, because some NSAID(s) are light sensitive and require a light protecting layer.

In still another alternative, the different active substances are dry mixed and filled into a capsule. In the latter preparation the acid susceptible proton pump inhibitor is in the form of

enteric coating layered units and the NSAID(s) is/are in the form of granules or alternatively in the form of modified release formulated units such as enteric coating layered units or units layered with a controlled release layer.

- 5 The NSAID(s) may be formulated in instant release, sustained release or extended release formulations. Alternatively, the components may be formulated in an effervescent formulation. Furthermore, as some NSAID(s) are light sensitive the formulation is preferably light protected by a pigmented tablet filmcoating layer, as exemplified in Fig. 6, or by including a pigment in one of the coating layers to be applied on the tableted dosage
10 form.

A further object of the invention is to provide a dosage form which is divisible, such as divisible tablets.

- 15 Still a further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. Some of the multiple unit tableted dosage forms may be dispersed in a slightly acidic aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

20

The different active components used in the present dosage forms are defined below.

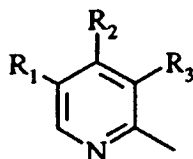
Active substances

- 25 The anti-ulcer drug is preferably an acid susceptible proton pump inhibitor. Such proton pump inhibitors are for example compounds of the general formula I

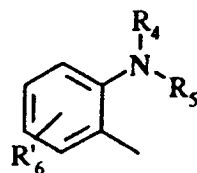


wherein

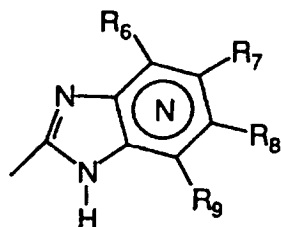
Het₁ is



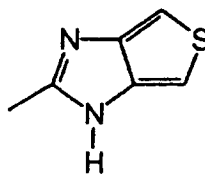
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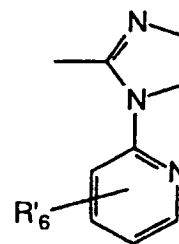
5 Het₂ is



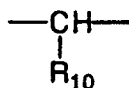
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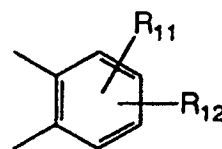
or



X =



or



wherein

10

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

15 R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

20 R'₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

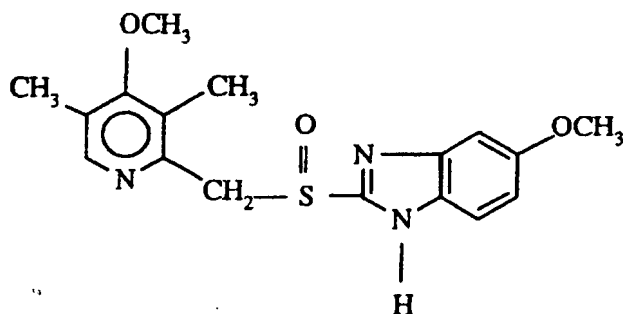
R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6 - R_9 form ring structures which may be further substituted;

- 5 R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C_1 - C_9 - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

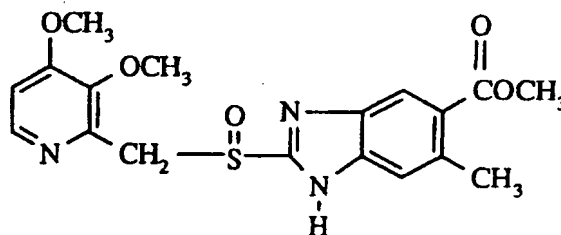
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Examples of proton pump inhibitors according to formula I are

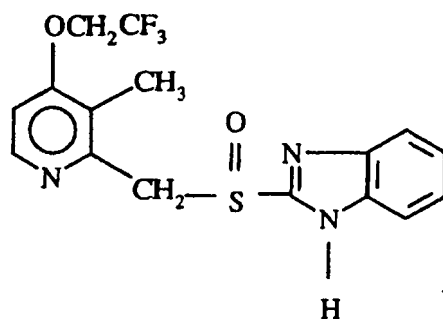
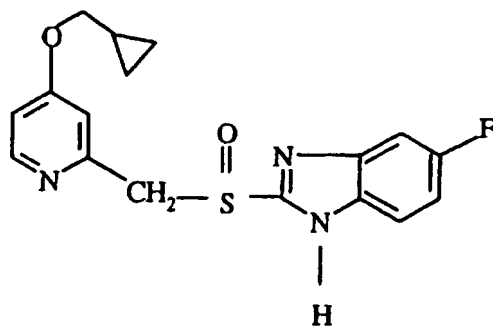


Omeprazole

15

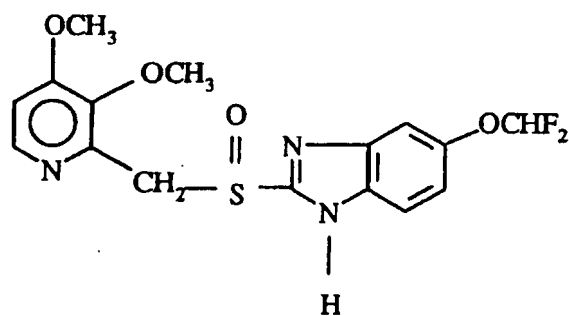


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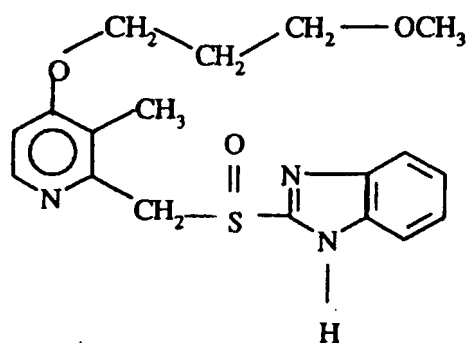


Lansoprazole

5

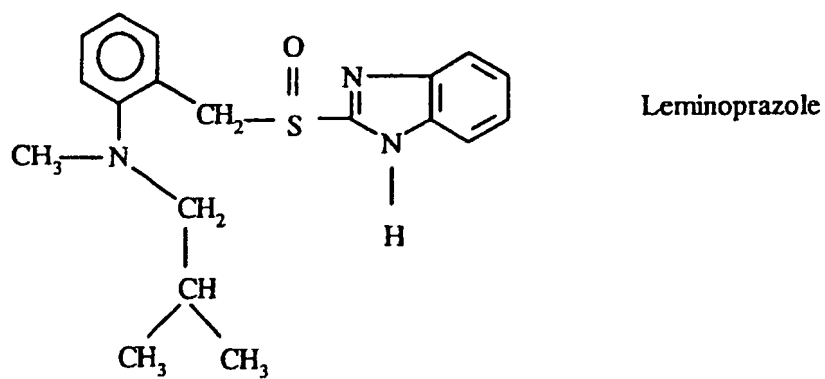


Pantoprazole

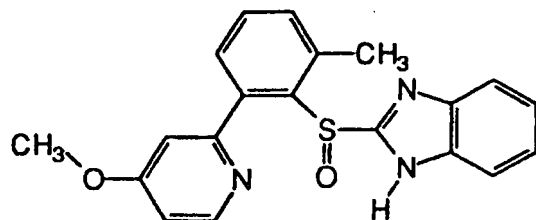
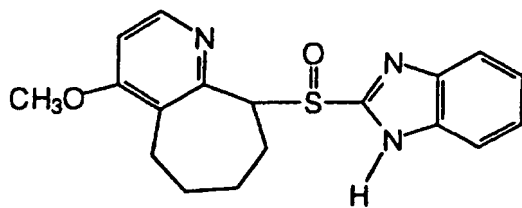
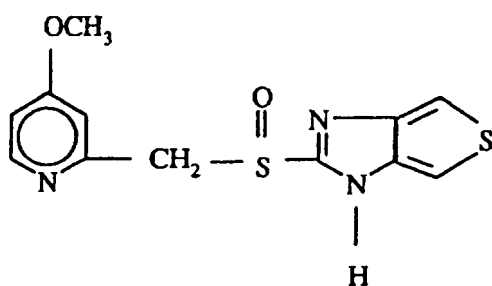


Pariprazole

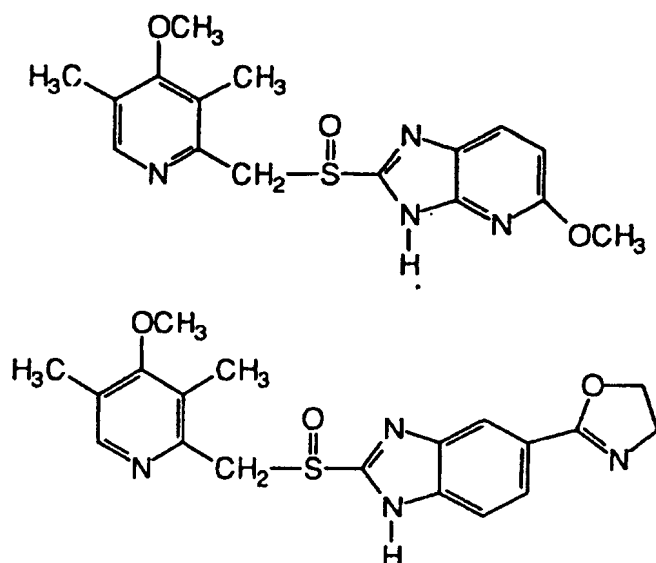
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5



10



The acid susceptible proton pump inhibitors used in the dosage forms of

5 the invention may be used in their neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of the substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

10 Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO94/27988.

15 A wide variety of NSAIDs may be used in combination with a suitable proton pump inhibitor and optional pharmaceutically acceptable excipients in the fixed unit dosage form according to the present invention. Such NSAIDs include for example propionic acid derivatives, oxicams, acetic acid and acetamide derivatives, salicylic acid derivatives and pyrazolidine derivatives.

Also future NSAIDs like cyclooxygenase (COX) 2 selective NSAIDs and NO-releasing NSAIDs (de Soldato P, NO-releasing NSAID:s, A new class of safer anti-inflammatory analgesic and anti-pyretic agents; The IV International meeting on side-effects of anti-inflammatory drugs August 7 - 9, 1995) may be included.

5

In the following examples of some suitable NSAIDs are listed: Acetyl salicylic acid, indometacin, diclofenac, piroxicam, tenoxicam, ibuprofen, naproxen, ketoprofen, nabumetone, ketorolac, azapropazone, mefenamic acid, tolfenamic acid, sulindac, diflunisal, tiaprofenic acid, podophyllotoxin derivatives, acemetacin, aceclofenac, droxicam,
10 oxaprozin, floctafenine, phenylbutazone, proglumetacin, flurbiprofen, tolmetin and fenbufen.

The active NSAIDs could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above listed drugs may be used. Preferable NSAIDs for the new fixed dosage form are diclofenac, ibuprofen, naproxen and piroxicam.

15

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor (in the form of a racemat, an alkaline salt or one of its single enantiomers) and one or more NSAIDs, is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the proton pump inhibitor and optionally
20 containing alkaline reacting substances, are mixed with the NSAID(s) and conventional tablet excipients. Preferably, the NSAID(s) and tablet excipients are in the form of a granulation. The dry mixture of enteric coating layered units, NSAID granules and optional excipients are compressed into multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, granules or pellets, in the following referred to as
25 pellets of the acid susceptible proton pump inhibitor.

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets comprising the acid susceptible proton pump inhibitor. In other words the mechanical
30 properties, such as the flexibility and hardness as well as the thickness of the enteric coating

layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid resistance does not decrease more than 10% during the compression of the pellets into tablets.

- 5 The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the
10 medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid Chromatography (HPLC).

- Further specific components which may be used in the fixed unit dosage forms of the
15 present invention are defined below.

Core material - for enteric coating layered pellets/units

- The core material for the individually enteric coating layered pellets can be constituted
20 according to different principles. Seeds layered with the proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

- The seeds which are to be layered with the proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or
25 in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or

solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl-cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), or sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

20

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the proton pump inhibitor in the final preparation. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives may be used.

25

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or

30

organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-
5 buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

10

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets, the pellets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline compounds such as pH-
15 buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). This/these separating layer(s) protecting the core material of proton pump inhibitor should be water soluble or rapidly disintegrating in water.

20 The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as,
25 for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium, water soluble salts of enteric coating polymers and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium
30 dioxide, talc and other additives may also be included into the separating layer(s).

- When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.
- Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material and an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a water soluble salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.
- One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers,

cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

5 The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

10 The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so
15 that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be
20 included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material. To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20
25 μm . The maximum thickness of the applied enteric coating is normally only limited by processing conditions and the desired dissolution profile.

The enteric coating layer may also be used for layering of the NSAID(s). Alternatively, the enteric coating layer described above may also be used for an enteric coating layer of
30 conventional tablets comprising a composition of a proton pump inhibitor and one or more

NSAIDs, optionally the prepared tablet core also is covered by one of the separating layers described above to separate the tablet core from the enteric coating layer.

Over-coating layer

5

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further it may protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions and the desired dissolution profile. The over-coating layer may also be used as a tablet filmcoating layer.

25 NSAID preparation

The active substance(s) in the form of one or more NSAID substances is dry mixed with inactive excipients, wherein one or more of the excipients optionally is a disintegrant. The mixture is wet massed with a granulation liquid. The wet mass is dried preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for

- the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients for the NSAID granulation are for instance, sodium starch glycolate, corn starch, crosslinked polyvinylpyrrolidone, low substituted hydroxypropyl cellulose, microcrystalline cellulose, mannitol and colloidal silicon dioxide anhydrous (Aerosil®) and the like. The dry mixture comprising NSAID(s) is mixed with a suitable granulation liquid comprising for instance, polyvinyl pyrrolidone, hydroxypropyl cellulose, polyethylene glycol, hydroxypropyl cellulose and optionally wetting agents, such as sodium lauryl sulphate, dissolved in purified water or a suitable alcohol or a mixture thereof.
- 10 Mechanical treatment may in some cases be used to form a complex between the NSAID(s) and a complex forming agent, such as beta-hydroxypropyl cyclodextrin like in Example 3 below. Cyclodextrin complexes of NSAID(s) are shown to have an increased bioavailability of the NSAID(s), see for instance Drug Dev. Ind. Pharm. 19(7), 843-852,(1993).
- 15 Further, the NSAID may be mixed with a gelling agent during the granulation, such as hydrophilic polymer(s). Suitable gelling hydrophilic polymers are for instance hydroxypropylmethylcellulose, polyoxyethylen (polyethylene glycol), hydroxypropylcellulose, hydroxyethylcellulose and xantan. The granules may also comprise buffering substances. See for instance Example 4 below. Some NSAIDs irritate the gastric mucosa and benefit from a protecting enteric coating layer and may be formulated as enteric coating layered pellets.
- 20

Multiple unit tablets

- 25 The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the granules comprising NSAID(s) and tablet excipients. The mixture is compressed into a multiple unit tableted dosage form. The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet filmcoating layer may further comprise additives such as anti-tacking agents, colorants and pigments or other
- 30

additives to obtain a tablet of good appearance and with a light-protection for light sensitive components.

The enteric coated pellets with or without an over-coat and the NSAID granules are mixed
5 with tablet excipients such as fillers, binders, disintegrants, lubricants and other
pharmaceutically acceptable additives and compressed into tablets. Suitable lubricants for
the tableting process are for instance sodium stearyl fumarate, magnesium stearate and talc.

Alternatively, the NSAID(s) may be dry mixed with the enteric coating layered pellets
10 comprising the proton pump inhibitor optionally together with inactive excipients and
compressed into tablets (direct compression), or the different active substances may be
formulated in different layers, optionally the NSAID(s) in the form of a layer with a
controlled release.

15 Further, both the NSAID(s) and the proton pump inhibitor in the form of enteric coating
layered pellets may be mixed with inactive tablet excipients and compressed into a tablet.
The compressed tablet is optionally covered by a tablet filmcoating layer to obtain a tablet
of good appearance.

20 As a further alternative a multiple unit tableted dosage form comprising the proton pump
inhibitor is spray coating layered by a suspension or solution comprising the NSAID(s). The
prepared tablet is thereafter covered by a pigmented tablet filmcoating layer.

The fraction of enteric coating layered pellets constitutes less than 75 % by weight of the
25 total tablet weight and preferably less than 60 %. By increasing the amount of the granules
comprising the NSAID(s) the fraction of enteric coating layered proton pump inhibitor
pellets in the multiple unit dosage form may be reduced. By choosing small enteric coating
layered pellets in the formulation according to the present invention, the number of pellets in
each tablet can be held high which in turn makes the tablet divisible with retained dosing
30 accuracy.

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of an acid susceptible proton pump inhibitor, optionally mixed with alkaline reacting compound(s), compressed into tablet
5 together with granules containing NSAID(s) and optionally tablet excipients. The addition of an alkaline reacting material to the proton pump inhibitor is not necessary, in any sense but such a substance may further enhance the stability of the proton pump inhibitor or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating layer. The enteric coating layer(s) is making the pellets of the dosage form
10 insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the proton pump inhibitor is desired. The NSAID(s) may be released in the stomach. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the tablet and they may also contain one or more
15 separating layer(s) in between the core material and the enteric coating layer.

Process

The process for the manufacture of the dosage form represents a further aspect of the
20 invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and then with the enteric coating layer(s) or a separating layer is spontaneously developed in situ between an alkaline core material and the enteric coating layer material. The coating is
25 carried out as described above and in the accompanying examples. The preparation of the granules comprising the NSAID(s) and enteric coating layered NSAID pellets are also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

The enteric coating layered pellets, with or without an over-coat, are mixed with the prepared granules, tablet excipients and other pharmaceutical acceptable additives and compressed into tablets. Alternatively, the different active substances in the form of powders may be intimately dry mixed with tablet excipients, wet massed and compressed
5 into conventional tablets before applying an optional separating layer and an enteric coating layer. The NSAID(s) may also be incorporated in a coating layer applied onto a multiple unit dosage form comprising the proton pump inhibitor, or the NSAID(s) and proton pump inhibitor in the form of enteric coating layered pellets are mixed with inactive tablet excipients and compressed into a multiple unit tableted dosage form.

10

The different active substances may also be formulated into different layers, wherein the layer comprising the NSAID(s) may be in the form of a control release preparation. As a further alternative, the acid susceptible proton pump inhibitor in the form of enteric coating layered pellets may be filled in a capsule together with the NSAID(s) in the form of granules
15 or enteric coating layered pellets, and optionally mixed with pharmaceutical excipients.

Use of the preparation

The dosage forms according to the invention are especially advantageous in the treatment of
20 gastrointestinal side-effects caused by NSAID(s), such as in a continuous treatment with NSAID(s). The new dosage forms are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0,1-200 mg of the
25 proton pump inhibitor and 0,1 - 1 000 mg of the NSAID(s). Preferably, each dosage form will comprise 10-80 mg of the proton pump inhibitor and 10-800 mg of the NSAID(s), and more preferably 10-40 mg of proton pump inhibitor and 10-500 mg of the NSAID(s), respectively. Especially preferred combinations comprise for instance 10 mg omeprazole together with 50 mg diclofenac, 10 mg omeprazole and 250 mg naproxen, 10 mg
30 omeprazole and 10 mg piroxicam, or 10 mg omeprazole and 400 mg ibuprofen.

The multiple unit tablet preparation may also be suitable for dispersion in an aqueous liquid with slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

5

The invention is illustrated more in detail in the following examples.

Examples

10 Example 1:

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole and ibuprofen.

15 Core material

Magnesium omeprazole	12.00 kg
Non-pareil cores	12.00 kg
Hydroxypropyl methylcellulose	1.8 kg
Water purified	35.4 kg

20

Separating layer

Core material (acc. to above)	23.50 kg
Hydroxypropyl cellulose	2.35 kg
Talc	4.03 kg
25 Magnesium Stearate	0.34 kg
Water purified	48.00 kg

Enteric coating layer

Pellets with sep layer (acc. to above)	29.00 kg
30 Methacrylic acid copolymer (30% suspension)	38.70 kg

	Triethyl citrate	3.48 kg
	Mono- and diglycerides (NF)	0.58 kg
	Polysorbate 80	0.06 kg
	Water purified	22.68 kg
5		
	<u>Over-coating layer</u>	
	Enteric coating layered pellets (acc. to above)	44.7 kg
	Hydroxypropyl methylcellulose	0.58 kg
	Mg-Stearate	0.017 kg
10	Water purified	11.6 kg
	<u>Tablets</u>	<u>mg/tablet</u>
	Over-coated pellets comprising omeprazole	47.85
	Ibuprofen	400
15	Microcrystalline cellulose (MCC)	273.6
	Polyvinylpyrrolidone cross-linked	100.4
	Polyvinylpyrrolidone K-25	33.3
	Sodium laurylsulphate	26.7
	Water purified	297
20	Sodium stearyl fumarate	4.0

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert non-pareil cores from a water suspension containing the dissolved binder.

- 25 The prepared core material was coating layered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the pellets (layered with a separating layer) in a fluid bed apparatus. In the same type of apparatus the enteric coating layered pellets

were coated with hydroxypropyl methylcellulose/Mg-Stearate suspension. The obtained pellets were classified by sieving.

Tablet granulation liquid was made by dissolving 26.7 parts of sodium laurylsulphate and 33.3 parts of polyvinylpyrrolidone K-25 in 267 parts of purified water. 400 parts of ibuprofen, 226 parts of the MCC and 10.4 parts of the cross-linked polyvinylpyrrolidone were dry-mixed. The granulating liquid was added to the powder mixture and the mass wet-mixed. 30 parts of water was added as quantum satis.

The wet mass was dried in an oven at 60°C for approx. 6 hrs. The dried granules were milled to pass a 0.8 mm sieve.

The enteric coating layered omeprazole pellets, the milled ibuprofen granules, 47.6 parts of MCC, 4.0 parts sodium stearyl fumarate and 90 parts of crosslinked polyvinylpyrrolidone were mixed and compressed to tablets on a tableting machine equipped with 15 mm diameter punches. Hardness of the 886 mg tablets tested with a Schleuniger apparatus varied between 5.3 and 5.9 kP. Disintegration time tested in simulated gastric juice (USP, without enzymes) was 49-52 sec (n=2).

20

Example 2

Fast disintegrating multiple unit tableted dosage form comprising S-omeprazole magnesium salt and naproxen.

25

Core material

S-omeprazole magnesium	120 g
Non-pareil cores	150 g
Polysorbat 80	2.4 g
Hydroxypropyl methylcellulose	18 g

	Water purified	562 g
	<u>Separating layer</u>	
	Core material (acc. to above)	200 g
5	Hydroxypropyl cellulose	30 g
	Talc	51.4 g
	Magnesium Stearate	4.3 g
	Water purified	600 g
10	<u>Enteric coating layer</u>	
	Pellets with sep layer (acc. to above)	250 g
	Methacrylic acid copolymer 30% suspension	333.7 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5.0 g
15	Polysorbate 80 (=Tween 80)	0.5 g
	Water purified	195.8 g
	<u>Over-coating layer</u>	
	Enteric coating layered pellets	371 g
20	Carboxymethylcellulose-sodium	5.0 g
	Water purified	191 g
	<u>Tablets</u>	<u>mg/tablet</u>
	Over-coated pellets comprising	
25	S-omeprazole Mg-salt	55
	Naproxen	250
	Microcrystalline cellulose (MCC)	150
	Hydroxypropylcellulose, low substituted	40
	Polyvinylpyrrolidone K-90	5.0
30	Water purified	250

Suspension layering was performed in a fluid bed apparatus. S-omeprazole magnesium salt was sprayed onto inert sugar seeds (non-pareil cores) from a water suspension containing the dissolved binder and polysorbat 80.

5

The prepared core material was coating layered by a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the pellets (with separating layer) in a fluid
10 bed apparatus. In the same type of apparatus the enteric coating layered pellets were covered with carboxymethylcellulose-sodium solution. The over-coating layered pellets were classified by sieving.

5 parts of polyvinylpyrrolidone K-90 was dissolved in 150 parts of purified water to form
15 the granulation liquid. Naproxen, MCC, and low-substituted hydroxypropyl cellulose were dry-mixed. The granulating liquid was added to the powder mixture and the mass wet-mixed. 100 parts of water was added as quantum satis.

The wet mass was dried in an oven at 60°C for approx. 5-6 hrs. The dried granules were
20 milled to pass a 1.0 mm sieve.

The enteric coating layered pellets and the milled granules were mixed and compressed to tablets on a tableting machine equipped with 18x8.5 mm punches. Average hardness for the 500 mg tablets tested (across the longest axis) with a Schleuniger apparatus was 9.4 kP.
25 Disintegration time tested in purified water at 37 °C was 15-30 sec (n=2).

Example 3

Fast disintegrating multiple unit tableted dosage form comprising pantoprazole and
30 piroxicam- β -hydroxypropyl-cyclodextrin.

Core material

	Pantoprazole	100 g
	Non-pareil cores	200 g
5	Hydroxypropylcellulose LF	25 g
	Water purified	607 g

Separating layer

	Core material (acc. to above)	200 g
10	Hydroxypropyl cellulose LF	20 g
	Talc	34.3 g
	Magnesium Stearate	2.9 g
	Water purified	400 g

15 Enteric coating layer

	Pellets with sep layer (acc. to above)	200 g
	Methacrylic acid copolymer, 30% suspension	333 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g
20	Polysorbate 80	0.5 g
	Water purified	281.5 g

Tabletsmg/tablet

	Pellets comprising pantoprazole	133
25	Piroxicam	20
	β -hydroxypropyl-cyclodextrin, (90%)	72
	Microcrystalline cellulose (MCC)	276
	Polyvinylpyrrolidone cross-linked	36.8
	Water purified	≤ 2

Sodium stearyl fumarate (SSF)

3.9

Suspension layering was performed in a fluid bed apparatus. Pantoprazole was sprayed onto
5 inert sugar seeds (non-pareil cores) from a water suspension containing the dissolved
binder.

The prepared core material was coating layered by a separating layer in a fluid bed
apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate.
10 The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides,
triethylcitrate and polysorbate was sprayed onto the pellets (with a separating layer) in a
fluid bed apparatus. The pellets were classified by sieving.

The piroxicam was added to β -hydroxypropyl-cyclodextrin during mechanical treatment and
15 moisturization with the water. The mass was dried in a drying oven at 50°C and then milled
to pass a 0.8 mm sieve.

The piroxicam- β -hydroxypropyl-cyclodextrin, the MCC, the cross-linked
polyvinylpyrrolidone and the SSF were dry-mixed and thereafter this mixture was mixed
20 with the pantoprazole pellets.

Compression to tablets was done on a tableting machine equipped with 18x8.5 mm
punches. Average hardness for the 577 mg tablets tested with a Schleuniger apparatus was
16.7 kP with variation between 14.8 and 18.7 kP, measurement taken along the longest
25 axis. Disintegration time tested in water was approx. 4 minutes.

The tablets were coated with a pigmented dispersion like in Ex. 7.

Example 4

Two-layered tablet dosage form with fast disintegrating part having 20 mg of lansoprazole in the form of enteric coated pellets comprised in one layer, and the other layer being an extended release part designed as a hydrophilic gel matrix comprising 250 mg of naproxen.

Lansoprazole enteric coated pelletsCore material

10	Lansoprazole	400 g
	Non-pareil cores	400 g
	Hydroxypropyl methylcellulose	80 g
	Sodium laurylsulphate	3 g
	Water purified	1360 g

15

Sub-coating

	Core material (acc. to above)	100 g
	Hydroxypropyl methylcellulos	9 g
	Polyethyleneglycol 6000	1 g
20	Talc	18 g
	Ethanol 95%	250 g
	Water purified	250 g

Enteric coating

25	Sub-coated pellets (acc. to above)	100 g
	Hydroxypropyl methylcellulose phtalate	39.9 g
	Acetyltributyl citrate	8 g
	Cetanol	2.1 g
	Ethanol 95%	162 g
30	Acetone	378 g

Suspension layering was performed in a fluid bed apparatus. Lansoprazole was sprayed onto inert non-pareil cores from a water suspension containing the dissolved binder and the wetting agent.

The prepared core material was sub-coated in a Wurster equipped fluid bed apparatus with the talc suspended in a HPMC/PEG- solution. PEG also have a function as plasticizer for the HPMC.

Enteric coating was performed in the same equipment with a solution in organic solvents of the materials forming the enteric layer.

	<u>Tablets</u>	<u>mg/tablet</u>
15	Pellets comprising lansoprazole	94
	Microcrystalline cellulose	181.8
	Polyvinyl pyrrolidone cross-linked	18.2
	Naproxen	250
	Polyoxyethylene (mwt appr. 4000000)	200
20	Sodium aluminium silicate	50
	L-Arginine	190
	Ethanol 95% (w/v) approx.	280

25 Naproxen, Polyox WSR 301®, L-Arginin and sodium aluminium silicate were dry-mixed. The granulating liquid, ethanol, was added to the powder mixture and the mass wet-mixed. The wet mass was dried in an oven at 60°C for approx. 8 hrs. The dried granules were milled to pass a 1.0 mm sieve.

Tablet compression was made by first pre-compressing 690 mg of the naproxen-containing granules and then filling 281 mg of a mixture consisting of 81 mg lansoprazole pellets plus 181.8 mg of MCC and 18.2 mg of crosslinked polyvinylpyrrolidone per tablet, on top.

These materials were then compressed together to give the two-layered tablets on a Diaf
5 tableting machine equipped with 9x20 mm punches. Tablet hardness tested with a
Schleuniger apparatus over the longest axis was approximately 14 kP.

Naproxen dissolution was tested in phosphate buffer pH 6.8. Obtained results;

	1 hrs	14% dissolved	
10	3 hrs	34%	"
	5 hrs	58%	"
	7 hrs	79%	"
	24 hrs	102%	"

15 Example 5

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole and piroxicam.

20 Core material (omeprazole)

Magnesium omeprazole	5.00 kg
Non-pareil cores	10.00 kg
Hydroxypropyl methylcellulose	0.75 kg
Water purified	19.65 kg

Separating layer (omeprazole)

	Core material (acc. to above)	14.60 kg
	Hydroxypropyl cellulose	1.46 kg
	Talc	2.5 kg
5	Magnesium Stearate	0.21 kg
	Water purified	29.2 kg

Enteric coating layer (omeprazole)

	Pellets with sep layer(acc. to above)	9.00 kg
10	Methacrylic acid copolymer (30% suspension)	15.00 kg
	Triethyl citrate	1.35 kg
	Mono- and diglycerides (NF)	0.22 kg
	Polysorbate 80	0.02 kg
	Water purified	8.8 kg

15

Over-coating layer (omeprazole)

	Enteric coating layered pellets	9.0 kg
	Hydroxypropyl methylcellulose	0.18 kg
	Mg-Stearate	0.005 kg
20	Water purified	3.6 kg

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert sugar seeds (non-pareil cores) from a water suspension containing the dissolved binder.

25

The prepared core material was coating layered by a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the sub-coated pellets in a fluid bed apparatus. In the same type of apparatus the enteric coating layered pellets were covered

30

with hydroxypropyl methylcellulose/Mg-Stearate suspension. The over-coating layered pellets were classified by sieving.

Core material (piroxicam)

5	Piroxicam micronized	35 g
	Sugar seeds	100 g
	Hydroxypropyl methylcellulose 6 cps	25 g
	Water purified	250 g
	Ethanol 99% (w/v)	250 g

10

Enteric coating layer (piroxicam)

	Piroxicam pellets (acc. to above)	100 g
--	-----------------------------------	-------

15

were coated with a suspension of the following composition to give a product with a content of 163 mg/g;

	Hydroxypropyl methylcellulose acetatesuccinate LF	14.38 parts
	Triethyl citrate	2.87 parts
	Sodium laurylsulphate	0.43 parts
20	Talc	4.32 parts
	Water purified	183.3 parts

25

Suspension layering was performed in a fluid bed apparatus. Micronized piroxicam was sprayed onto inert non-pareil cores from a water suspension containing the dissolved binder.

The enteric coating layer consisting of hydroxypropyl methylcellulose acetatesuccinate, triethylcitrate, sodium laurylsulphate and talc was sprayed onto the piroxicam pellets in a fluid bed apparatus.

Tablets (for 1000 pcs)

	pellets comprising omeprazole	95.7 g
	pellets containing piroxicam	122.7 g
5	Microcrystalline cellulose (MCC)	240 g
	Polyvinylpyrrolidone cross-linked (PVP-XL)	20 g
	Hydroxypropylcellulose, low-substituted (L-HPC)	40 g
	Sodium stearyl fumarate (SSF)	4.6 g
10	MCC, L-HPC and PVP-XL were mixed together until homogeneity. The two kind of enteric coating layered pellets were admixed thereafter. Finally the lubricant SSF was admixed and this mixture was compressed to tablets on a tableting machine equipped with 8.5x16 mm punches. Hardness of the 523 mg tablets tested with a Schleuniger apparatus varied between 8 and 9 kP. Disintegration time tested in water 37°C was less than 1 minute	

15

The tablets were coated with a pigmented dispersion like in Example 7.

Example 6

- 20 Fast disintegrating enteric coating layered tablet comprising magnesium omeprazole and diclofenac.

Tablets (for 2000 pcs)

	Omeprazole magnesium (corr. 20 mg omeprazole)	45.0 g
25	Diclofenac sodium (corr. 20 mg diclofenac)	43.2 g
	Microcrystalline cellulose (MCC)	110 g
	Polyvinylpyrrolidone cross-linked (PVP-XL)	50 g
	Hydroxypropylcellulose, low-substituted (L-HPC)	50 g
	Sodium stearyl fumarate (SSF)	8.6 g
30	Water purified	approx. 170 g

The omeprazole, diclofenac, MCC, L-HPC, 30 grams of PVP-XL and 5.6 grams of SSF were mixed and then the water was added during continuously mixing. The granulate was dried in a drying oven at 60°C for approx. 1.5 hours. The dry granulate was milled to pass
5 sieve 1.0 mm.

The milled granules were mixed with 20 grams of PVP-XL and 3.0 grams of SSF. This mixture was compressed to 153 mg tablets on a tableting machine using 7 mm diameter punches. Average tablet hardness was 7.4 kP (n=6). Disintegration time in water 37°C was
10 1 minute 20 seconds (n=1).

The tablets were coating layered with a separating layer consisting of hydroxypropyl methylcellulose (HPMC) and talc in a Wurster equipped fluidized bed.

15 Application of separating layer

	Tablets 7 mm	100.1 g
	coating dispersion;	
20	HPMC 6 cps	5.5 g
	Talc	1.15 g
	EtOH 99%(w/v)	46.7 g
	Water purified	46.7 g
25	The obtained coating layered tablets were further coating layered by an enteric coating layer in the same apparatus.	

Application of enteric coating layer

Tablets with separating layer 100 g

5 coating dispersion;

Methacrylic acid copolymer as 30% suspension 26.4 g (7.92 g dry mtrl.)

Polyethyleneglycole 400 0.9 g

Titanium dioxide 0.83 g

Iron oxide reddish brown 0.28 g

10 Water purified 55.1 g

The weight increase of the tablets in the enteric coating step was approx. 11 mg/tablet, corresponding to approx. 7% of the weight of charged tablets.

15 The pigments in the enteric coating layer provides protection against light.

Example 7

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole
20 and an inner coating layer comprising diclofenac-sodium and an outer pigmented coating layer providing light protection.

Magnesium omeprazole enteric coating layered pellets from Ex. 5.

25 <u>Tablets</u>	<u>mg/tablet</u>
Pellets comprising omeprazole	83.3
Microcrystalline cellulose (MCC)	181.4
Polyvinylpyrrolidone cross-linked	3.7
Sodium stearyl fumarate (SSF)	0.4

Pellets were prepared as in Example 5.

The MCC, the cross-linked polyvinylpyrrolidone and the omeprazole containing pellets were dry-mixed. Thereafter the SSF was admixed.

5

The mixture was compressed to tablets on a tableting machine equipped with 9 mm diameter punches. Hardness of the 269 mg tablets tested with a Schleuniger apparatus varied between 8 and 9 kP.

10 The tablets were coated in a fluidized bed with the solution below, until average tablet weight was 298 mg.

	Diclofenac-sodium	20.0 parts by weight
	HPMC 6 cps	11.4 parts by weight
15	EtOH 99%(w/v)	113.6 parts by weight
	Water purified	113.6 parts by weight

Finally these tablets were covered with pigmented suspension in the same equipment. The composition of the coating suspension was;

20

	HPMC 6 cps	10 parts by weight
	Polyethylene glycol mwt 6000	2.5 parts by weight
	TiO ₂	1.83 parts by weight
	Iron oxide yellow	0.40 parts by weight
25	EtOH 99%(w/v)	85 parts by weight
	Water purified	85 parts by weight

Obtained average tablet weight was 303 mg. Disintegration time tested in water 37°C was less than 4 minutes (n=4).

30

Example 8

A capsule formulation comprising magnesium omeprazole and piroxicam.

5 Capsules

Enteric coating layered omeprazole pellets

(manufacturing and composition as in Ex. 5) 95.7mg/cap

Enteric coating layered piroxicam pellets

(manufacturing and composition as in Ex. 5) 122.7mg/cap

10

Prepared pellets are filled into hard gelatine capsules, size 3. Optionally a small amount of lubricant is added before filling into capsules. The amount of omeprazole in each capsule is approx. 20 mg and the amount of piroxicam is approx. 20 mg.

15 Example 9

A capsule formulation comprising S-omeprazole magnesium salt and naproxen.

Capsules

20 Enteric coating layered pellets

(manufacturing and composition as in Ex. 2) 55.2mg/cap

Naproxen granulation

(manufacturing and composition as in Ex. 2) 445mg/cap

25 Prepared granules and enteric coating layered pellets are filled into hard gelatine capsules, size 00. Optionally a small amount of lubricant is added before filling into capsules. The amount of S-omeprazole in each capsule is approx. 10 mg and the amount of naproxen is approx. 250 mg.

Example 10:

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole and diclofenac-Na.

5

Core material

	Magnesium omeprazole	5 kg
	Sugar sphere seeds	10 kg
	Hydroxypropyl methylcellulose	0.75 kg
10	Water purified	19.7 kg

Separating layer

	Core material	10.2 kg
	Hydroxypropyl cellulose	1.02 kg
15	Talc	1.75 kg
	Magnesium stearate	0.146 kg
	Water purified	21.4 kg

Enteric coating layer

20	Pellets covered with separating layer	11.9 kg
	Methacrylic acid copolymer (30 % suspension)	19.8 kg
	Triethyl citrate	1.79 kg
	Mono- and diglycerides (NF)	0.297 kg
	Polysorbate 80	0.03 kg
25	Water purified	11.64 kg

Over-coating layer

	Enteric coating layered pellets	20.0 kg
	Hydroxypropyl methylcellulose	0.238 kg
30	Magnesium stearate	0.007 kg

Water purified 6.56 kg

<u>Tablets</u>	<u>mg/tablet</u>
Overcoated pellets comprising omeprazole	82.4
5 Diclofenac-Na	50.0
Microcrystalline cellulose (MCC)	261
Polyvinylpyrrolidone cross-linked	5.6
Sodium stearyl fumarate	0.56

- 10 Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.
- The prepared core material was covered with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid
- 15 copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with a hydroxypropyl methylcellulose solution containing magnesium stearate. The over-coating layered pellets were classified by sieving.
- 20 The enteric coating layered pellets with an over-coating layer, diclofenac-Na, MCC, polyvinylpyrrolidone cross-linked and sodium stearyl fumarate were dry mixed and compressed into tablets using an excenter tableting machine equipped with 11 mm punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of diclofenac-Na was approx. 50 mg. The tablet hardness was measured to 80 N.

25

Example 11:

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole and piroxicam.

Core material

	Magnesium omeprazole	10.0 kg
	Sugar sphere seed	10.0 kg
	Hydroxypropyl methylcellulose	1.5 kg
5	Water purified	29.9 kg

Separating layer

	Core material	20.0 kg
	Hydroxypropyl cellulose	2.0 kg
10	Talc	3.43 kg
	Magnesium stearate	0.287 kg
	Water purified	41.0 kg

Enteric coating layer

15	Pellets covered with separating layer	24.5 kg
	Methacrylic acid copolymer (30 % suspension)	32.7 kg
	Triethyl citrate	2.94 kg
	Mono- and diglycerides (NF)	0.49 kg
	Polysorbate 80	0.049 kg
20	Water purified	19.19 kg

Over-coating layer

	Enteric coating layered pellets	37.8 kg
	Hydroxypropyl methylcellulose	0.49 kg
25	Magnesium stearate	0.0245 kg
	Water purified	11.6 kg

Tablets

		<u>mg/tablet</u>
	Overcoated pellets comprising omeprazole	94.9
30	Piroxicam	20.0

Microcrystalline cellulose (MCC)	280
Polyvinylpyrrolidone cross-linked	5.6
Sodium stearyl fumarate	0.56

- 5 Enteric coating layered pellets of magnesium omeprazole with an overcoating layer were prepared as in Example 10.

The enteric coating layered pellets with an over-coating layer, piroxicam, MCC, polyvinylpyrrolidone cross-linked and sodium stearyl fumarate were dry mixed and
 10 compressed into tablets using an excenter tableting machine equipped with 11 mm punches. The amount of omeprazole in each tablet was approx. 20 mg and the amount of piroxicam was approx. 20 mg. The tablet hardness was measured to 110 N.

Results

"Acid resistance" i.e. % left after exposure to 0.1 N HCl for 2 hrs	
	Tablets
Ex 1	95%
Ex 2	95%
Ex 3	99%
Ex 4	91%
Ex 5	92%
Ex 6	96%
Ex 7	93%
Ex 10	91%
Ex 11	91%

The best mode to practice the present invention is according to the dosage forms of the types described in examples 5, 7 and 10.

- 5 The enteric coating layered pellets comprising a proton pump inhibitor may also be prepared as described in the following examples.

Example 12

- 10 Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material

	Magnesium omeprazole	600 g
	Mannitol	1000 g
15	Microcrystalline cellulose	300 g
	Hydroxypropyl cellulose	100 g
	Sodium lauryl sulphate	6 g
	Water purified	802 g

20 Separating layer

	Core material (acc. to above)	400 g
	Hydroxypropyl methylcellulose	48 g
	Water purified	960 g

25 Enteric coating layer

	Pellets covered with separating layer (acc. to above)	200 g
	Methacrylic acid copolymer	100 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g

Polysorbate 80	0.5 g
Water purified	309 g

Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid.

- 5 Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

- The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The
10 extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

- 15 The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

20 Example 13

Preparation of enteric coating layered pellets by powder layering of sugar sphere seeds.

Core material

25 Magnesium omeprazole	1 500 g
Sugar sphere seeds	1 500 g
Hydroxypropyl methylcellulose	420 g
Aerosil®	8 g
Water purified	4 230 g

Separating layer

	Core material (acc. to above)	500 g
	Hydroxypropyl cellulose	40 g
	Talc	67 g
5	Magnesium stearate	6 g
	Water purified	800 g

Enteric coating layer

	Pellets covered with separating layer (acc. to above)	500 g
10	Methacrylic acid copolymer	200 g
	Triethyl citrate	60 g
	Water purified	392 g

Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-
15 mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder
in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose
solution (6 %, w/w).

The prepared core material is dried and covered by a separating layer in a centrifugal
20 fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layering.

Example 14

Preparation of enteric coating layered pellets with cores of silicon dioxide seeds.

25

Core material

	Magnesium omeprazole	8.00 kg
	Silicon dioxide	8.00 kg
	Hydroxypropyl methylcellulose	1.41 kg
30	Sodium lauryl sulphate	0.08 kg

Water purified 28.00 kg

Separating layer

Core material (acc. to above) 10.00 kg

5 Hydroxypropyl methylcellulose 0.80 kg

Water purified 10.00 kg

Enteric coating layer

Pellets covered with separating layer (acc. to above) 300 g

10 Methacrylic acid copolymer 124 g

Polyethylene glycol 400 25 g

Mono- and diglycerides (NF) 3 g

Polysorbate 80 1 g

Water purified 463 g

15

Suspension layering is performed in a fluid bed apparatus. Magnesium orneprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved binder and a surface active ingredient.

20 The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

25 Example 15

Preparation of enteric coating layered pellets.

Enteric coating layer

30 Pellets covered with separating layer

(manufacturing and composition

as in example 12)

500 g

Methacrylic acid copolymer

250 g

Polyethylene glycol 6000

75 g

5 Mono- and diglycerides (NF)

12.5 g

Polysorbate 80

1.2 g

Water purified

490 g

Example 16

10

Preparation of enteric coating layered pellets.

Enteric coating

Pellets covered with separating layer

500 g

15 (manufacturing and composition as in example 1)

Hydroxypropyl methylcellulose phthalate

250 g

Cetanol

50 g

Ethanol (95%)

1000 g

Acetone

2500 g

20

Example 17

Preparation of enteric coating layered pellets.

25 Core material

Omeprazole

225 g

Mannitol

1425 g

Hydroxypropyl cellulose

60 g

Microcrystalline cellulose

40 g

30 Lactose anhydrous

80 g

Sodium lauryl sulphate	5 g
Disodium hydrogen phosphate dihydrate	8 g
Water purified	350 g

5 Separating layer

Core material (acc. to above)	300 g
Hydroxypropyl cellulose	30 g
Talc	51 g
Magnesium stearate	4 g

10

Enteric coating layer

Pellets covered with separating layer (acc. to above)	300 g
Methacrylic acid copolymer	140 g
Triethyl citrate	42 g
15 Mono- and diglycerides (NF)	7 g
Polysorbate 80	0.7 g

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm. The prepared core material is covered with a separating layer and enteric coating layered as described in previous examples.

25

Preparation of active substance.

Magnesium omeprazole used in some of the examples is produced according to the process described in WO/95/01977, the single enantiomers of omeprazole salts are prepared as

described in WO/94/27988 and omeprazole is produced according to the process disclosed in EP-A1 0005129. These documents are hereby incorporated in a whole by reference.

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with at least one Non Steroidal Antiinflammatory Drug (NSAID) and
5 optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components, and wherein at least the proton pump inhibitor is protected by an enteric coating layer.
- 10 2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.
3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.
- 15 4. A dosage form according to claim 1, wherein the proton pump inhibitor is protected by two layers, an enteric coating layer and a layer separating the enteric coating from the proton pump inhibitor.
- 20 5. A dosage form according to claim 1, wherein the dosage form comprises a proton pump inhibitor and one NSAID.
6. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole, an alkaline salt thereof, one of its single enantiomer or an alkaline salt thereof.
- 25 7. A dosage form according to claim 6, wherein the proton pump inhibitor is S-omeprazole magnesium salt.
8. A dosage form according to claim 1, wherein the proton pump inhibitor is
30 lansoprazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.

9. A dosage form according to claim 1, wherein the proton pump inhibitor is pantoprazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.

5 10. A dosage form according to one of claims 6 - 9, wherein the NSAID is ibuprofen, diclofenac, piroxicam or naproxen, or a pharmaceutical acceptable salt thereof.

11. A dosage form according to one of claims 6 - 9, wherein the NSAID is diclofenac or piroxicam, or pharmaceutically acceptable salt thereof.

10

12. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-80 mg and the amount of NSAID(s) is in the range of 10-800 mg.

13. A dosage form according to claim 1, wherein the amount of proton pump inhibitor
15 is in the range of 10-40 mg and the amount of NSAID(s) is in the range of 10-500 mg.

14. A tableted dosage form according to claim 2, wherein the tablet consists of two separate layers, one layer comprising a proton pump inhibitor and the other layer comprising one or more NSAIDs.

20

15. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the proton pump inhibitor in the form of individually enteric coating layered pellets compressed together with NSAID comprising granules into a tablet, whereby the enteric coating layer covering the individual pellets has
25 mechanical properties such that the tableting of the pellets together with the NSAID comprising granules and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the individually enteric coating layered pellets.

16. A tableted dosage form according to claim 15, wherein the acid resistance of the enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.
- 5 17. A tableted dosage form according to claim 15, wherein the acid resistance of the enteric coating layered pellets does not decrease more than 10 % during the compression of the pellets into the multiple unit tableted dosage form.
18. A tableted dosage form according to claim 15, wherein the enteric coating of the
10 individual pellets comprises a plasticized enteric coating layer material.
19. A tableted dosage form according to claim 15, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.
- 15 20. A tableted dosage form according to claim 15, wherein the tablet is divisible.
21. A tableted dosage form according to claim 20, wherein the tablet is dispersible to an aqueous suspension comprising NSAID(s) and enteric coating layered pellets of a proton
20 pump inhibitor.
22. A tablet dosage form according to claim 2, wherein the tablet consists of two separate layers, one layer comprising the proton pump inhibitor in the form of enteric coating layered pellets compressed with tablet excipients into a layer, and the other layer
25 gives an extended release of the incorporated NSAID(s).
23. A tablet dosage form according to claim 22, wherein the layer comprising the NSAID(s) is a gelling matrix giving extended release.

24. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating layered tablet comprising a mixture of the proton pump inhibitor and the NSAID comprising granules, optionally comprising a water soluble or in water rapidly disintegrating separating layer in between the tablet core and the enteric coating layer.
- 5 25. A tableted dosage form according to claim 2, wherein the tablet comprising enteric coating layered pellets of the proton pump inhibitor compressed into a tablet, which tablet is covered by a separate layer comprising the NSAID(s).
- 10 26. A tableted dosage form according to claim 25, wherein the tablet is covered by a pigmented tablet filmcoating layer.
27. A tablet dosage form according to claim 2, wherein the tablet consists of two types of enteric coating layered pellets, one type comprises the proton pump inhibitor, and the
15 other type comprises NSAID(s), together compressed with tablet excipients into a tablet.
28. A tablet dosage form according to claim 2, wherein the tablet consists of enteric coating layered pellets comprising the proton pump inhibitor, and pellets comprising the NSAID(s) coating layered with an extended release film, and these coating layered pellets
20 are compressed with tablet excipients into a tablet.
29. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAIDs in a capsule, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and that the pellets are
25 filled into a capsule together with prepared NSAID granules or enteric coating layered NSAID pellets, or NSAID pellets coating layered with an extended release film, optionally the mixture of pellets or granules are mixed with pharmaceutically acceptable excipients, and filled in a capsule.

30. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAIDs in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with prepared NSAID granules and optionally pharmaceutically acceptable tablets excipients whereafter the dry mixture is compressed into a multiple unit
5 tablet without giving any significant change of the acid resistance of the enteric coating layer.

31. A process for the manufacture of a fixed dosage form comprising a proton pump
10 inhibitor and one or more NSAIDs in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and the NSAID(s) is prepared in the form of coating layered pellets wherein the coating layer is an extended release layer or an enteric coating layer, and the prepared pellets are mixed with tablet excipients and compressed into a tablet.

15 32. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAID(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with the NSAID(s) and pharmaceutically acceptable excipients whereafter the mixture is compressed into a tablet, and the tablet is
20 covered with an enteric coating layer and optionally covered with a separating layer before the enteric coating layer is applied.

33. A method for the treatment of gastrointestinal side-effects associated with NSAID treatment in mammals and man by administering to a host in need thereof a therapeutically
25 effective dose of a multiple unit tableted dosage form according to any of claims 1 to 28.

34. A method according to claim 33, wherein the disorder is an upper gastrointestinal disorder associated with NSAID treatment.

35. Use of a dosage form according to any of claims 1 to 28 for the manufacture of a medicament for treatment or prevention of gastro intestinal side-effects associated with NSAID(s) treatment disorders.
- 5 36. Use according to claim 35 wherein the disorder is an upper gastrointestinal disorder associated with NSAID treatment.

1 / 2

Fig. 1

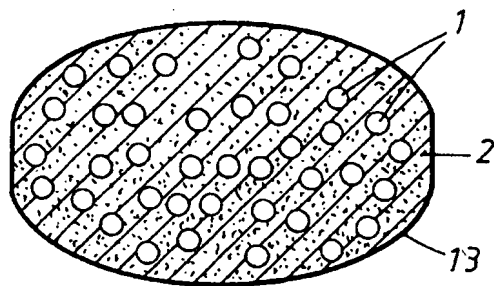


Fig. 2

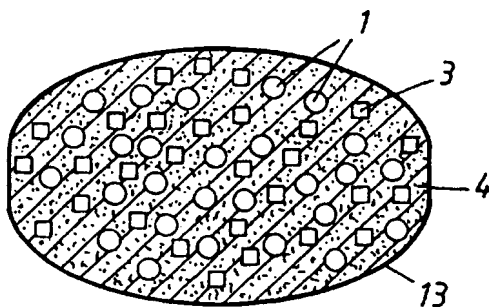


Fig. 3

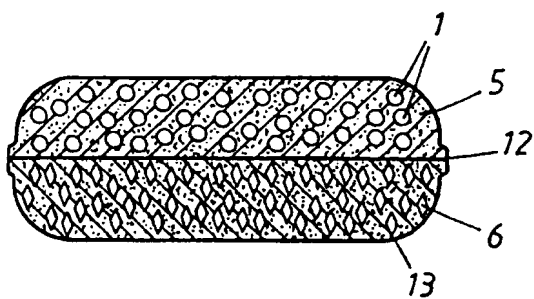


Fig. 4

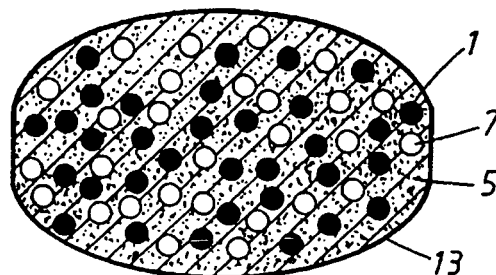


Fig. 5

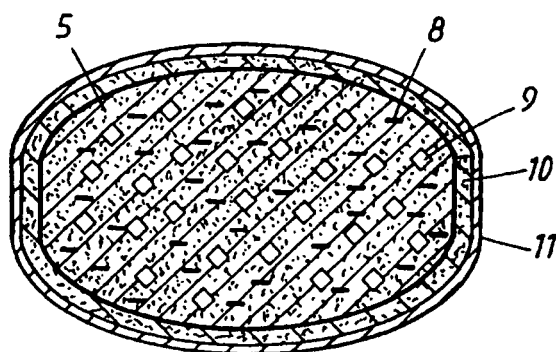
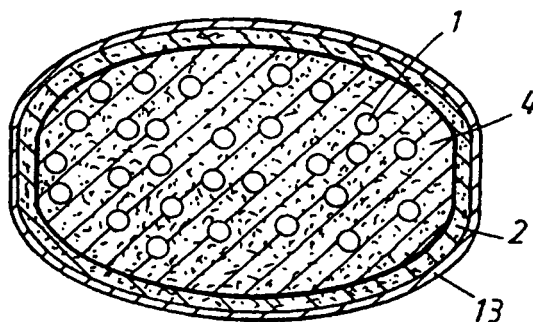


Fig. 6



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01735

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/44, A61K 31/19, A61K 31/54, A61K 9/26, A61K 9/54
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, US FULLTEXT, WPI, WPIL, CLAIMS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0426479 A1 (MCNEIL-PPC, INC.), 8 May 1991 (08.05.91) --	1-36
A	STN International, File CAPLUS, CAPLUS accession no. 1992:187668, Scheiman, James M. "Pathogenesis of gastroduodenal injury due to nonsteroidal antiinflammatory drugs", Semin. Arthritis Rheum. (1992), 21(4), 201-10 --	1-36
A	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 4, line 25 - page 5, line 2; page 8, line 22 - line 32 --	12-36

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

9 April 1997

Date of mailing of the international search report

22.04.97

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01735

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90), page 3, line 41 - line 46; page 4, line 42 - line 57 -- -----	12-36

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01735

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 33-34
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 33-34 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.

PCT/SE 96/01735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.

PCT/SE 96/01735

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